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**ALKANOLAMINES TO
ANTIBIOTICS**

CONTENT INDEX (vol 2)
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ALKANOLAMINES

Alkanolamines from olefin oxides and ammonia ,
Alkanolamines from nitro alcohols,

ALKANOLAMINES FROM OLEFIN OXIDES AND AMMONIA

Ethylene oxide [75-21-8], propylene oxide [75-56-9], or butylene oxide [106-88-7] react with ammonia to produce alkanolamines (Table 1). Ethanolamines, NH₂-_n (C₂H₄OH)_n (*n* = 1, 2, 3, mono-, di-, and tri-), are derived from the reaction of ammonia with ethylene oxide. Isopropanolamines, NH₂-_n (CH₂CHOHCH₃)_n (mono-, di-, and tri-), result from the reaction of ammonia with propylene oxide. Secondary butanolamines, NH₂-_n (CH₂CHOHCH₂CH₃)_n (mono-, di-, and tri-), are the result of the reaction of ammonia with butylene oxide. Mixed alkanolamines can be produced from a mixture of oxides reacting with ammonia.

Table 1. Physical Properties of Alkanolamines Prepared from Ammonia and Olefin Oxides

Common name	Molecular formula	CAS Registry Number	Chemical Abstracts name
monoethanolamine (MEA)	C ₂ H ₇ NO	[141-43-5]	2-aminoethanol
diethanolamine (DEA)	C ₄ H ₁₁ NO ₂	[111-42-2]	2,2'-iminobisethanol
triethanolamine (TEA)	C ₆ H ₁₅ NO ₃	[102-71-6]	2,2',2''-nitrilotrisethanol
monoisopropanolamine (MIPA)	C ₃ H ₉ NO	[78-96-6]	1-amino-2-propanol
diisopropanolamine (DIPA)	C ₆ H ₁₅ NO ₂	[110-97-4]	1,1'-iminodi-2-propanol
triisopropanolamine (TIPA)	C ₉ H ₂₁ NO ₃	[122-20-3]	1,1',1''-nitrilotris-2-propanol
mono- <i>sec</i> -butanolamine	C ₄ H ₁₁ NO	[13552-21-1]	1-amino-2-butanol
di- <i>sec</i> -butanolamine	C ₈ H ₁₉ NO ₂	[21838-75-5]	1,1'-iminodi-2-butanol
tri- <i>sec</i> -butanolamine	C ₁₂ H ₂₇ NO ₃	[2421-02-5]	1,1',1''-nitrilotris-2-butanol

^a At 101.3 kPa = 1 atm.
^b Approximate, at 25°C unless otherwise noted.
^c Supercools; freezing points may show variation.

Structural formula	Freezing point, °C	Boiling point, °C	Water solubility, g/100 g	<i>n</i> -Heptane solubility ^b , g/100 g	Viscosity ^b , mPa·s (= cP)
NH ₂ C ₂ H ₄ OH	10	171	∞	0.06	19
NH(C ₂ H ₄ OH) ₂	28	268	∞	0.01	54 (60°C)
N(C ₂ H ₄ OH) ₃	21	340	∞	0.02	600
NH ₂ CH ₂ CHOHCH ₃	3 ^c	159	∞	0.4	23
NH(CH ₂ CHOHCH ₃) ₂	44 ^c	249	1200	0.1	86 (54°C)
N(CH ₂ CHOHCH ₃) ₃	44 ^c	306	>500	3.4	100 (60°C)
NH ₂ CH ₂ CHOHC ₂ H ₅	3	169	∞	0.04	29
NH(CH ₂ CHOHC ₂ H ₅) ₂	68–70	256	∞	4.7	890
N(CH ₂ CHOHC ₂ H ₅) ₃	41–47	310	ca 7	>100	ca 6000

Ethanolamines have been commercially available for over 50 years and isopropanolamines, for over 40 years. *sec*-Butanolamines have been prepared in research quantities, but are not available commercially. Primary butanolamines, eg, 2-amino-1-butanol [96-20-8] are made by a different chemical route (see ALKANOLAMINES FROM NITROALCOHOLS).

A variety of substituted alkanolamines are also available commercially, but have not reached the volume popularity of the ethanolamines and isopropanolamines (see Table 2).

Table 2. Physical Properties of Substituted Alkanolamines

Common name	Molecular formula	CAS Registry Number
dimethylethanolamine	C ₄ H ₁₁ NO	[108-01-0]
diethylethanolamine	C ₆ H ₁₅ NO	[100-37-8]
aminoethylethanolamine (AEEA)	C ₄ H ₁₂ N ₂ O	[111-41-1]
methylethanolamine	C ₃ H ₉ NO	[109-83-1]
butylethanolamine	C ₆ H ₁₅ NO	[111-75-1]
<i>N</i> -acetyethanolamine	C ₄ H ₉ NO ₂	[142-26-7]
phenylethanolamine	C ₈ H ₁₁ NO	[122-98-5]
dibutylethanolamine	C ₁₀ H ₂₃ NO	[102-81-8]
diisopropylethanolamine	C ₈ H ₁₉ NO	[96-80-0]
phenylethylethanolamine	C ₁₀ H ₁₅ NO	[92-50-2]
methyldiethanolamine	C ₅ H ₁₃ NO ₂	[105-59-9]
ethyldiethanolamine	C ₆ H ₁₅ NO ₂	[139-87-7]
phenyldiethanolamine	C ₁₀ H ₁₅ NO ₂	[120-07-0]

dimethylisopropanolamine	C ₅ H ₁₃ NO	[108-61-7]
N-(2-hydroxypropyl)ethylenediamine	C ₅ H ₁₄ N ₂ O	[123-84-2]

^a At 101.3 kPa = 1 atm unless otherwise noted.
^b Approximate, at 25°C.
^c At 20°C unless otherwise noted.
^d Pour point.
^e Sets to a glasslike solid below this temperature.
^f Melting point.
^g At 8 kPa (60 mm Hg).

Chemical Abstracts name	Freezingpoint t, °C	Boilingpoint ^a , °C	Watersolubility ^b g/100 g ^a	Viscosity ^c , mPa·s(= cP)
2-dimethylaminoethanol	−59	135	∞	3
2-diethylaminoethanol		162	∞	4
2-(2-aminoethylamino)ethanol	−38 ^d	244	∞	141
2-methylaminoethanol	−4.5	160	∞	13
2-butylaminoethanol	−2	199	∞	20
N-2-hydroxyethylacetamide	16	decompn	∞	203
2-anilinoethanol	11	285	4.6	101
2-dibutylaminoethanol	−75 ^e	229	0.4	8
2-diisopropylaminoethanol	−39	191	1.2	8
2-N-ethylanilinoethanol	37 ^f	decompn	0.2	
2,2'-(methylimino)diethanol	−21	247	∞	101
2,2'-(ethylimino)diethanol	< −44 ^e	253	∞	87
2,2'-(phenylimino)diethanol	57 ^d		2.8	119 (60°C)
1-dimethylamino-2-propanol	−85 ^e	126		
1-(2-aminoethylamino)-2-propanol	−50 ^e	155 ^g	∞	112 (25°C)

Physical Properties

The freezing points of alkanolamines are moderately high as shown in Tables 1 and 2. The ethanolamines, monoisopropanolamine and mono-*sec*-butanolamine, are colorless liquids at or near room temperature. Di- and triisopropanolamine and di- and tri-*sec*-butanolamine are white solids at room temperature.

All the ethanolamines and isopropanolamines except monoisopropanolamine are available in low freezing grades, to provide liquid handling at room temperature.

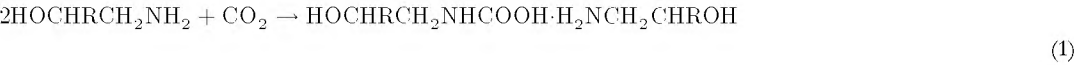
Alkanolamines have a mild ammoniacal odor and are extremely hygroscopic (1). The mono- and dialkanolamines have a basicity similar to aqueous ammonia; the trialkanolamines are slightly weaker bases.

All the alkanolamines, except tri-*sec*-butanolamine, are completely miscible in water and polar solvents. Solubility in nonpolar solvents varies, as noted in Tables 1 and 2.

Chemical Reactions

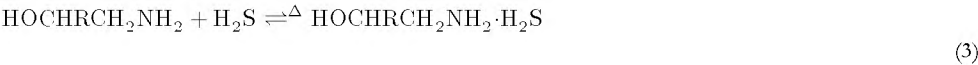
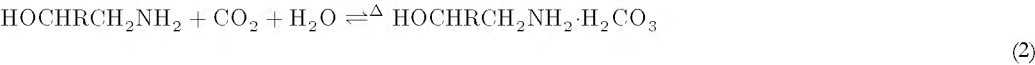
Alkanolamines are bifunctional molecules because of the alcohol and the amine functional groups in the same compound. This allows them to react in a wide variety of ways, with similarities to primary, secondary, and tertiary amines, and primary and secondary alcohols.

Reaction with Acids. Under anhydrous conditions, mono- and diethanolamines and isopropanolamines form carbamates with carbon dioxide (2,3).

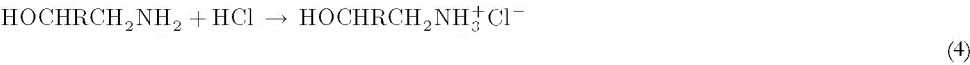


Trialkanolamines, lacking an amine hydrogen, do not undergo the carbamate reaction.

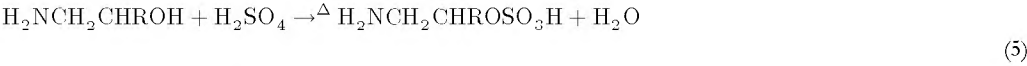
Alkanolamines in aqueous solution react with carbon dioxide and hydrogen sulfide to yield salts, important to gas conditioning reactions. The dissociation of the salts upon heating results in recovery of the original starting material. These reactions form the basis of an important industrial application, ie, the "sweetening" of natural gas.



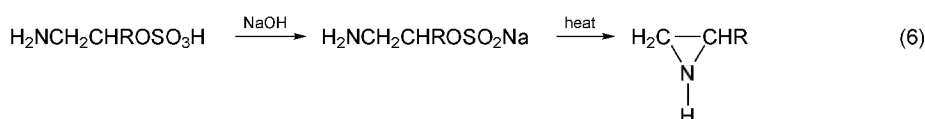
Halogen acids and strong organic acids, such as *p*-nitrobenzoic acid and trichloroacetic acid, form crystalline salts (4), with alkanolamines.



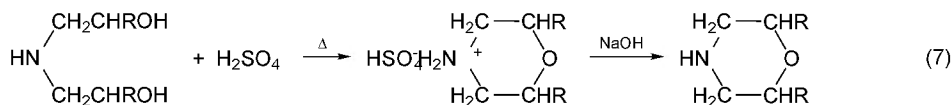
Heating with sulfuric acid gives bisulfates (5).



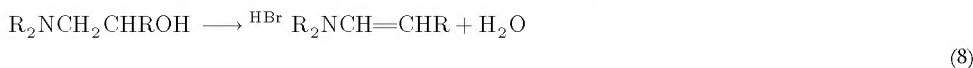
These can be cyclized by heating in the presence of sodium hydroxide to give a dehydration product. Thus monoalkanolamines form 2-alkylaziridines.



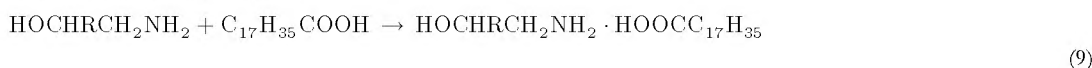
In a similar manner, diethanolamine and diisopropanolamine can be cyclized to give morpholines (6).



Nitric acid gives nitrates and concentrated (48%) hydrobromic acid gives olefins, upon reaction with alkanolamines.



Reaction with Fatty Acids and Esters. Alkanolamines and long-chain fatty acids react at room temperature to give neutral alkanolamine soaps, which are waxy, noncrystalline materials with widespread commercial applications as emulsifiers. At elevated temperatures, 140–160°C, *N*-alkanolamides are the main products, at a 1:1 reaction ratio (7,8).

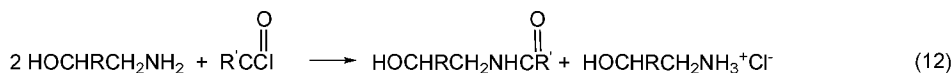


Significant quantities of amine and amide esters are formed by side reactions (9). In addition, with dialkanolamines, amide diesters, morpholines, and piperazines can be obtained, depending on the starting material. Reaction of dialkanolamines with fatty acids in a 2:1 ratio, at 140–160°C, produces a second major type of alkanolamide. These products, in contrast to the 1:1 alkanolamides, are water soluble; they are complex mixtures of *N*-alkanolamides, amine esters, and diesters, and still contain a considerable amount of unreacted dialkanolamine, accounting for the water solubility of the product. Both the 1:1 and the 2:1 alkanolamides are of commercial importance in detergents.

Trialkanolamines cannot form amides, but they do give esters at temperatures sufficiently high to eliminate water.



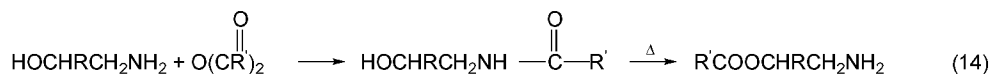
Reaction with Acyl Halides. Acyl halides react at room temperature with mono- and dialkanolamines to give amides (10,11).



At elevated temperatures, in the presence of alkali, mono-, di-, and trialkanolamines produce esters.



Reaction with Acid Anhydrides. Below room temperature, acid anhydrides react with alkanolamines to produce amides, which partially rearrange to esters on warming to room temperature or slightly above.



A 2:1 molar ratio of alkanolamine and fatty acid anhydride, at room temperature, gives a mixture of amide and alkanolamine soap.



Reaction with Aldehydes and Ketones. Formaldehyde combines with primary and secondary alkanolamines in the presence of alkali to give methylol derivatives. For the reaction of monoethanolamine with formaldehyde (12), the reaction scheme shown in Figure 1 occurs.

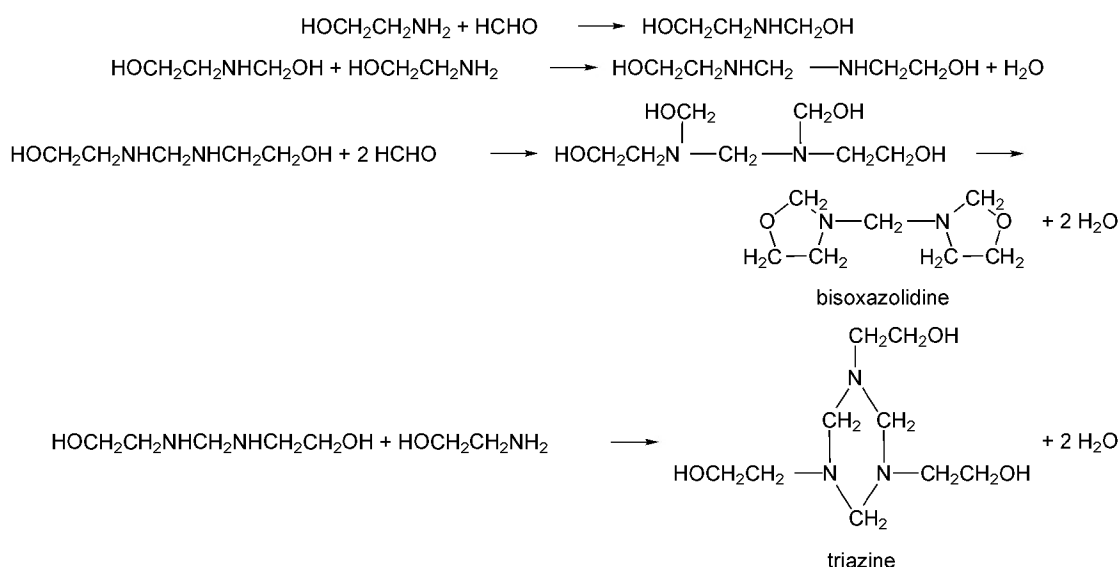
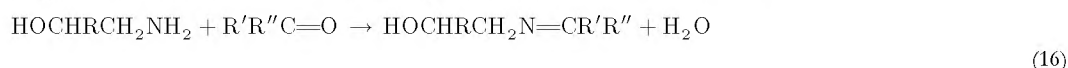


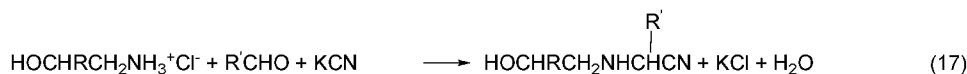
Fig. 1. Reaction of formaldehyde with monoethanolamine. If two moles of monoethanolamine react with three moles of formaldehyde, the bisoxazolidine is the only product isolated. A 1:1 mole ratio of monoethanolamine to formaldehyde produces a mixture of the triazine and the bisoxazolidine.

Primary alkanolamines react with aliphatic and aromatic aldehydes or ketones (other than formaldehyde) to give Schiff bases.



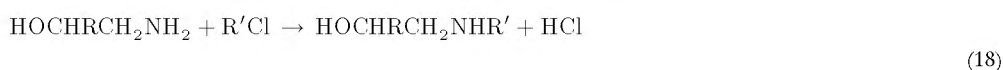
The Schiff bases can be catalytically hydrogenated to the corresponding saturated derivatives. More severe conditions cause cyclization to oxazolidines.

With secondary alkanolamines, aldehydes in the presence of K_2CO_3 yield di-tertiary amines, which, on distillation, break down into α,β -unsaturated amines and secondary amines. With a mono- or dialkanolamine, an alkali metal cyanide, and an aldehyde or ketone, aminoacetonitriles are formed.

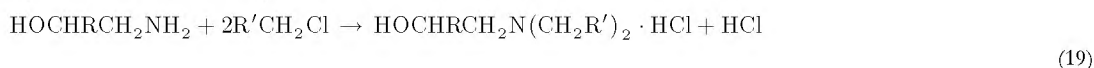


These nitriles can be saponified to the corresponding acids.

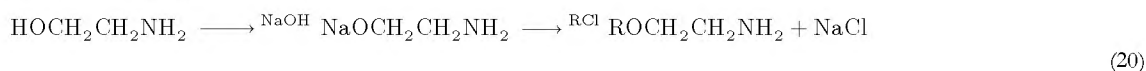
Reaction with Alkyl and Aralkyl Halides. Alkyl halides form *N*-alkyl derivatives of alkanolamines.



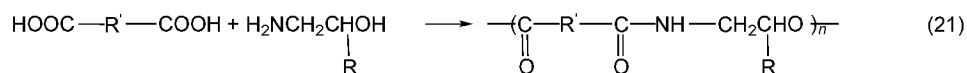
Aralkyl halides (R' either phenyl or naphthyl) give disubstituted products.



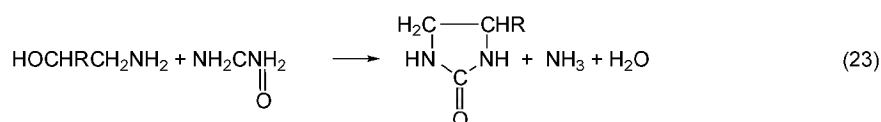
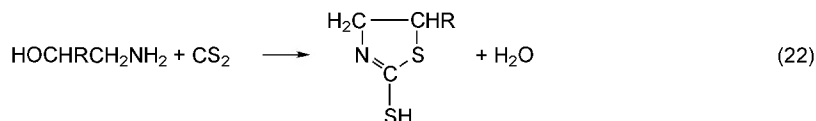
Mono- and dialkyl derivatives can also be prepared using alkyl sulfates. Aryl chlorides are usually inert, unless activated by an electron-withdrawing group. Conversion to alkoxides allows formation of ethers.



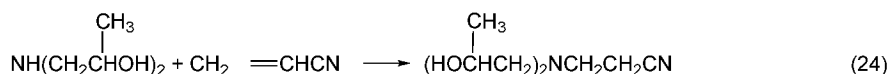
Other Reactions. Polyester polyamides can be formed from dicarboxylic acids (13).



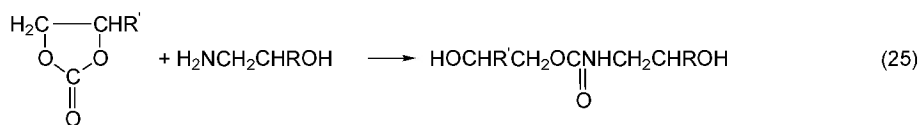
Monoalkanolamines are converted by carbon disulfide into 2-mercaptothiazolines. Ethyleneurea (2-imidazolidinone) can be prepared by heating a mixture of monoethanolamine and urea for several hours.



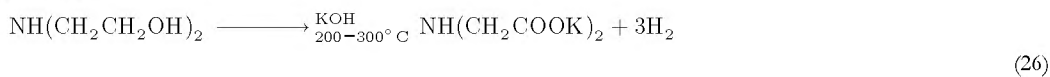
With acrylonitrile, mono- and dialkanolamines undergo a Michael addition to give the β -aminonitrile.



Mono- and dialkanolamines react readily with ethylene or propylene carbonates to yield carbamates.



Alkanolamines can be oxidized with various oxidizing agents. With acidic potassium permanganate or excess potassium hydroxide, the potassium salts of the corresponding amino acid are obtained.



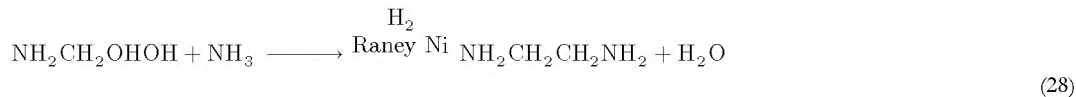
Mono- and diethanolamine are converted to formaldehyde and ammonia by acidic periodates.

Numerous patents exist for the production of nitrilotriacetic acid [139-13-9] and its salts from triethanolamine (14-16).



In certain cases, alkanolamines function as reducing agents. For example, monoethanolamine reduces anthraquinone to anthranols, acetone to 2-propanol, and azobenzene to aniline (17). The reduction reaction depends on the decomposition of the alkanolamine into ammonia and an aldehyde. Similarly, diethanolamine converts *o*-chloronitrobenzene to 2,2'-dichloroazobenzene and *m*-dinitrobenzene to 3,3'-diaminoazobenzene.

Monoethanolamine can also be reduced catalytically with hydrogen and ammonia over Raney nickel at 200°C and 20.7 MPa (3000 psig) to produce ethylenediamine [107-15-3] (18,19).



Manufacture

Alkanolamines are manufactured from the corresponding oxide and ammonia. Anhydrous or aqueous ammonia may be used, although anhydrous ammonia is typically used to favor monoalkanolamine production and requires high temperature and pressure (20). Mono-, di-, and trialkanolamines are produced in the reactor and sent to downstream columns for separation (Fig. 2).

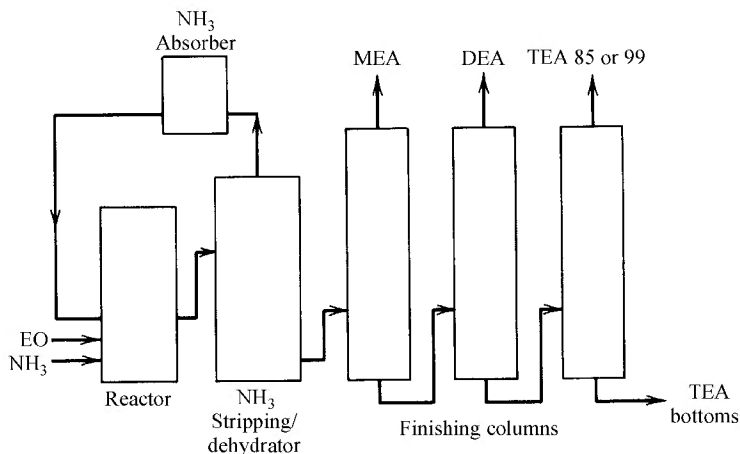
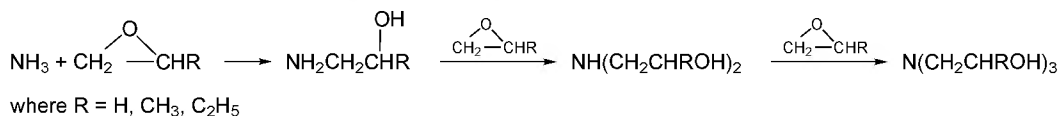


Fig. 2. Flow sheet for ethanolamine production. EO = ethylene oxide; MEA, DEA, and TEA are defined in Table 1.

The reaction is exothermic; reaction rates decrease with increased carbon number of the oxide (ethylene oxide > propylene oxide > butylene oxide). The ammonia-oxide ratio determines the product split among the mono-, di-, and trialkanolamines. A high ammonia to oxide ratio favors mono-production; a low ammonia to oxide ratio favors trialkanolamine production. Mono- and dialkanolamines can also be recycled to the reactor to increase di- or trialkanolamine production. Mono- and dialkanolamines can also be converted to trialkanolamines by reaction of the mono- and di- with oxide in batch reactors. In all cases, the reaction is run with excess ammonia to prevent unreacted oxide from leaving the reactor.

A variety of substituted alkanolamines (Table 2) can also be made by reaction of oxide with the appropriate amine. Aminoethylethanolamine is made from the reaction of ethylenediamine [107-15-3] and ethylene oxide. Methyl-diethanolamine is made from the reaction of ethylene oxide and methylamine [74-89-5]. Diethylethanolamine is made by the reaction of diethylamine [109-87-7] and ethylene oxide.

Economic Aspects

U.S. capacity of the ethanolamines in 1989, almost one-half of global capacity, was estimated to be 379,000 t. Global capacity for 1989 was estimated at 692,000 t. Estimated annual U.S. production figures are listed in Table 3 (21). U.S. consumption of ethanolamines for various applications is shown in Table 4.

Table 3. Estimated Annual U.S. Production of Ethanolamines, 10³ t

Year	Total	MEA	DEA	TEA
1955	36	12	14	10
1960	57	20	24	13
1965	91	31	35	25
1970	120	40	42	38

1975	118	38	39	41
1980	171	59	56	56
1985	245	98	76	71
1988	278	103	86	89
1990	302	113	91	98
1995	362	137	106	119

Table 4. U.S. Consumption by Use of Ethanolamines, 10³ t

Use	1950	1960	1970	1980	1990
surfactants, detergents, and personal care products	5.9	25.4	43	60	95
gas purification	1.8	13.2	23	35	30
textiles	1.8	9.1	6	4	5
agricultural products	2.7	1.1	2	4	4
cement and concrete			3	5	7
metal working	1.8	3.6	5	6	7
chemical processing intermediate			6	8	42
other	1.4	4.5	4	5	5

Isopropanolamine global capacity for 1989 was estimated at 37,000 t. U.S. capacities for isopropanolamine (IPA), aminoethylethanolamine (AEEA), and methyldiethanolamine (MDEA) are as follows:

Akanolamine	U.S. capacity, 10 ³ t
IPA	23,000
AEEA	9,000
MDEA	20,000

Consumption of ethanolamines in the United States has changed dramatically since the 1960s. Consumption in gas conditioning applications has peaked and chemical processing intermediates (captive use for ethyleneamine and surfactant applications) has increased significantly. U.S. production of ethanolamines grew at just under 8% during the 1980s. Export of ethanolamines has contributed significantly to the increased production. Exports have averaged 11% growth per year during the 1980s. U.S. sales consumption have grown an average of 6% a year since 1970. List pricing (22) has ranged from ~45/kg in the 1960s, to a low of 33¢/kg in the early 1970s. In the mid-1970s, the price increased to over 65¢/kg to peak in the early 1980s at over \$1.10/kg. Prices decreased again in the mid-1980s to peak again at \$1.43/kg in 1989 for bulk quantities.

Specifications

Specifications for the most commonly used alkanolamines are listed in Table 5. Special grades of products have been developed as needed by the customer. *National Formulary* grade meets the specifications in the *U.S. Pharmacopeia*. Low iron and electronic grades have particular specifications for iron and other metals. Low freezing grades were developed because of the high freezing points of most of the product. Generally, the addition of 15% water, by weight, significantly reduces the freezing point to a manageable level.

Table 5. Typical Specifications of Alkanolamines^a

Compound	Assay ^b , min %	Apparent ^c equivalent weight	APHA ^d colormax	Water, max %
MEA, CG ^e	99	61–62	15	0.3
DEA, CG ^e	99	104–106	15	0.15
TEA 85 ^f	85	140–145	40	0.20
TEA 99	99	148–150	50	0.2
MIPA	99	75–76	20	0.5
DIPA, CG ^e	98	132–134	40	0.5
TIPA 99	99	190–192	50	0.3
AEEA	99.6		25	0.2

^a Specification values and items may vary with different manufacturers. Analytical methods may be obtained from manufacturers.

^b Assay determined by gas chromatography.

^c Apparent equivalent weight determined by titration with hydrochloric acid.

^d APHA color determined by ASTM D1209, platinum–cobalt method.

^e CG = commercial grade.

^f Contains approximately 15% DEA.

Analytical Test Methods

Generally, alkanolamines are analyzed by gas chromatography or wet test methods. Details on gas chromatography conditions are available in the literature (1) for packed or glass capillary columns. Apparent equivalent weight can be determined by titration with hydrochloric acid using a bromocresol green indicator. Calculations give the equivalent weight of total amines and are not specific for the mono-, di- or trialkanolamines. APHA color is determined using ASTM D1209; percent water is determined by Karl Fischer titration following ASTM E203. Detailed analytical procedures are available in the literature (1) or from producers.

Storage and Handling

Stainless steel, 316L and 304L, is the preferred material of construction for shipment and storage of alkanolamines, if product quality is of importance. Aluminum can be used for short term transport, at temperatures below 60°C, for the pure amines. Plastic liners have not been found acceptable for all alkanolamines. Phosphatized-lined steel drums are used for transport of ethanlolamines and isopropanolamines, except MEA, which is shipped in high density polyethylene drums to maintain low product color. Monoethanolamine and monoisopropanolamine are classified as DOT corrosive liquids.

Polyethylene, polypropylene, and Teflon resins have been found to be acceptable in contact with all of the alkanolamines at low temperatures. Lined tanks have not been found to successfully withstand monoethanolamine and monoisopropanolamine. These two alkanolamines degrade all linings tested. Extensive testing of any lined tank or piping should be initiated before being used in any alkanolamine service. Some producers use only stainless steel in handling, storage, and shipping of their alkanolamines.

Mild steel can be used for transport and storage if product discoloration is not a problem, such as in gas conditioning applications. Contact with copper, brass, and other copper alloys may cause corrosion of the metal.

Storage tanks, lines, and pumps should be heat traced and insulated to enable product handling. Temperature control is required to prevent product degradation because of color; alkanolamines have poor heat transfer properties. Exposure to air will also cause product discoloration. Storage tanks should be nitrogen-padded if low color product is required.

Normally, centrifugal pumps, made of stainless steel, are used to transfer amines to maintain good product quality. Carbon steel or black iron pumps can be used if quality is unimportant. Heat tracing the pumps may also be required if exposure to cold weather is a possibility. Teflon gaskets and Teflon tape can be used for applications under 200°C. Graphite-filled gaskets can also be used. Graphite packing or mechanical seals with Teflon resins are also suggested. Alkanolamines can leach conventional pipe dope.

Reactions of monoethanolamine with mild steel are referenced in the literature (23). The complex formed, identified as trisethanolamino-iron, can decompose in air to pyrophoric iron, with the potential to cause a fire, if contacted with combustible materials.

Health and Safety

A brief summary of safety and health hazards follows; detailed health hazards, however, should be obtained from producers by requesting Material Safety Data Sheets. Proper protective equipment and exposure hazards should be noted before handling any alkanolamine. Detailed toxicological testing is found in the CTFA Chemical Ingredient Review Board Reports on ethanolamines and isopropanolamines (24).

Oral Toxicity. Alkanolamines generally have low acute oral toxicity, but swallowing substantial quantities could have serious toxic effects, including injury to mouth, throat, and digestive tract.

Concentrated monoethanolamine and monoisopropanolamine can cause severe local irritation or even burns to the mouth, throat, and digestive tract. If monoethanolamine and monoisopropanolamine are swallowed, large volumes of milk or water should be administered immediately. If diethanolamine, triethanolamine, diisopropanolamine, or triisopropanolamine are swallowed, vomiting should be induced after drinking two glasses of water.

Vapor Toxicity. Laboratory exposure data indicate that vapor inhalation of alkanolamines presents low hazards at ordinary temperatures (generally, alkanolamines have low vapor pressures). Heated material may cause generation of sufficient vapors to cause adverse effects, including eye and nose irritation. If inhalation exposure is likely, approved respirators are suggested. Monoethanolamine and diethanolamine have OSHA TLVs of 3 ppm.

Eye Irritation. Exposure of the eye to undiluted alkanolamines can cause serious injury. Solutions as dilute as 1% of monoethanolamine and monoisopropanolamine can cause some eye irritation.

Diethanolamine, diisopropanolamine, and isopropanolamine mixtures are also irritating to the eyes, even diluted, but less so than monoethanolamine and monoisopropanolamine. Undiluted triethanolamine and triisopropanolamine and concentrated solutions have an irritating action on the eyes, but only slight transient or no corneal injury would be expected. Proper protective equipment, as detailed in the Material Safety Data Sheets should be used. Chemical workers' goggles or the equivalent, and suitable facilities for washing the eyes should be readily available. If any of the amines contact the eyes, the eyes should be flushed thoroughly with flowing water for 30 min for monoethanolamines and isopropanolamines, and 15 min for di- and triethanolamines, and di- and triisopropanolamines.

Skin Irritation. Monoethanolamine and monoisopropanolamine, being strongly alkaline, are skin irritants, capable of producing serious injury in concentrations of 10% or higher upon repeated or prolonged contact. Occasional short contact, assuming the material is thoroughly washed off, should have little adverse effect.

Diethanolamine, diisopropanolamine, and isopropanolamine mixtures are less irritating to the skin than MEA and MIPA; however, any one of them may produce severe skin irritation, even mild burns, if contact is prolonged or frequently repeated. Occasional short contact should not result in more than slight irritation. Undiluted triethanolamine and triisopropanolamine are slightly to moderately irritating to the skin. A burn may result from prolonged and repeated contact. Short occasional contact and solutions of less than 10% concentration are unlikely to cause more than very slight irritation, if any.

Monoethanolamine and monoisopropanolamine may be moderately toxic by absorption through the skin. The other amines are low in toxicity by this route and are not likely to be absorbed in acutely toxic amounts. In the event of skin contact, clothing and shoes should be removed promptly, and the skin thoroughly washed with water. Contaminated clothing should be thoroughly cleaned before reuse; shoes and leather products should be discarded.

Special Precautions. Use of sodium nitrite or other nitrosating agents in formulations containing alkanolamines could lead to formation of suspected cancer-causing nitrosamines.

Strong oxidizers and strong acids are incompatible with alkanolamines. Reactions, generating temperature and or pressure increases, may occur with halogenated organic compounds. Alkanolamines are corrosive to copper and brass and may react. Contact with aluminum by alkanolamines, particularly when wet or at elevated temperatures (60°C), should be avoided.

Spills and leaks should be cleaned up with alkanolamine-compatible absorbents or sands. Local, state, and federal requirements should be followed for disposal. Incineration in an approved facility is suggested for final disposal.

Uses

Alkanolamines and their derivatives are used in a wide variety of household and industrial applications. Nonionic surfactants (alkanolamides) can be formed by the reaction of alkanolamines with fatty acids, at elevated temperatures (eq. 10). The amides can be liquid, water-soluble materials as produced from a 2:1 ratio, or solid, poorly water-soluble materials, or "super" amides as produced from a 1:1 ratio of reactants. These products are useful as foam stabilizers, and aid cleaning in laundry detergents, dishwashing liquids, shampoos, and cosmetics. They are also used as antistatic agents, glass coatings, fuel gelling agents, drilling mud stabilizers, demulsifiers, and in mining flotation. Reaction of alkanolamines with a fatty acid at room temperature produces neutral alkanolamine soaps (eq. 9). Alkanolamine soaps are found in cosmetics, polishes, metalworking fluids, textile applications, agricultural products, household cleaners, and pharmaceuticals.

Alkanolamine salts are anionic surfactants (qv) formed from the reaction of alkanolamines and the acids of synthetic detergents, such as alkylarylsulfonates, alcohol sulfates, and alcohol ether sulfates. These add to the surfactants line used in detergents, cosmetics, textiles, polishes, agricultural sprays, household cleaners, pharmaceutical ointments, and metalworking compounds. Salts of alkanolamines and inorganic acids are useful chemical intermediates (eq. 4), and are also used in corrosion inhibitors, antistatic agents, glass coatings, electroplating, high octane fuels, inks, metalworking, dust control in mining, and in textiles.

Adhesives. Alkanolamines are used in hot melt adhesives for binding nonpervious materials to polyolefins (25). Diethanolamine and triethanolamine have been used in the area of phenol formaldehyde adhesives to improve bond strengths (26,27), improve storage stability (28–30), and to increase water dispersibility (31). Starch-based adhesives have increased stability, viscosity, and gel temperature with the addition of monoethanolamine or diethanolamine to Mannich reaction products (32,33). Asphalt compositions have increased bonding to the aggregate in the emulsion when monoethanolamine is added (34,35). Refractory binder formulations, ceramics, and molds are improved by alkanolamine usage for stimulating gel

formation (36–38). Anaerobic adhesive sheets, useful in adhering to ABS resin sheets, are made from the combination of diethanolamine, epoxidized polybutadiene, and peroxide (39).

Cement and Concrete. Low concentrations of triethanolamine or its salts are added to cement clinkers to increase the efficiency of the grinding mill by reducing particle agglomeration (40). The resulting cement is more free-flowing and pack-set is reduced. The mechanism is presumed to be due to the dispersing capability of the triethanolamine, creating a uniform particle dispersion throughout the mixture.

In concrete, triethanolamine accelerates set time and increases early set strength (41–43). These are often formulated as admixtures (44), for later addition to the concrete mixtures. Compared to calcium chloride, another common set accelerator, triethanolamine is less corrosive to steel-reinforcing materials, and gives a concrete that is more resistant to creep under stress (45). Triethanolamine can also neutralize any acid in the concrete and forms a salt with chlorides. Improvement of mechanical properties, whiteness, and more even distribution of iron impurities in the mixture of portland cements, can be effected by addition of 2% triethanolamine (46). Triethanolamine bottoms and alkanolamine soaps can also be used in these type applications. Waterproofing or sealing concrete can be accomplished by using formulations containing triethanolamine (47,48).

Cleaners. Properties, such as foaming and detergency (qv), make alkanolamines useful in cleaning formulations. Monoethanolamine is particularly effective in wax removal formulations because of its ability to penetrate films. Cleaners that involve skin contact use triethanolamine because of its mildness. Derivatives of the amines (49,50) as well as the free alkanolamines (51–53), may be formulated into cleaning products.

Coatings. A wide variety of applications have been reported in coatings technology. The alkanolamines are added to neutralize polyester, epoxy (54–56), polyamide, and urethane (57) resin coatings to enhance dispersibility (58–60). In metal-coating preparations, the alkanolamines serve as complexing agents, neutralizers, promoters, modifiers, corrosion inhibitors, and electrophoretic bath components (61–62). Alkanolamines assist in improving adhesion, curing resins, complexing metals, improving storage stability, and improving both fresh and salt water resistance for some types of coatings (63–67).

Alkanolamines are used in urethane coatings for glass shatter proofing (68) and have been utilized as amides, salts, or free amines in providing antifrosting, antifogging, and dirt-resistant films on glass and plastics (69–72).

Triethanolamine and diethanolamine are accelerators for photopolymerization coatings (73–75). Diethanolamine is the most commonly used alkanolamine in the preparation of cationic polymers for electrophoretic coatings. The use of acrylate–amine–isocyanate–anhydride copolymers provides electrodeposited coatings that can be cured with uv light (76,77). All of the ethanolamines are effective in improving thermal properties and reducing cracking in prepared wire coatings (78–82).

Corrosion Inhibitors. Alkanolamines inhibit corrosion of ferrous metals (83). These can be used in a wide variety of applications, such as coolant systems, lubricating oils (84,85), metal working fluids, petroleum antifouling (86), and drilling needs (87). Monoethanolamine is most often used in applications requiring free base, and triethanolamine as a salt with organic and inorganic acids. Fatty acid salts are used in lubricating and metal working fluids (88), whereas inorganic salts, the phosphate or borate, are used in aqueous or mixed-solvent systems such as glycol antifreeze (89). Corrosion inhibitors for aluminum, containing alkanolamines, are also detailed in the literature (90).

Alkanolamines are also used in formulations for corrosion prevention. Triethanolamine-containing formulations can be used to coat stainless steel to prevent high temperature oxidation (91). Short term anticorrosion protection for metal parts during quenching can be accomplished by using triethanolamine salts of phosphoric acid esters (92,93). Rusted steel surfaces can be stabilized before painting, using triethanolamine-containing formulations in the prime paint (94).

It should be noted that corrosion inhibitors and protection systems are generally designed for specific conditions, and the effectiveness of the inhibitor can change with conditions.

Cosmetics and Personal Care Products. Alkanolamines are important raw materials in the manufacture of creams (95–97), lotions, shampoos, soaps, and cosmetics. Soaps (98) formed from triethanolamine and fatty acids are mild, with low alkalinity and excellent detergency. Triethanolamine lauryl sulfate is a common base for shampoos (99–101) and offers significant mildness over sodium lauryl sulfate. Diethanolamine lauryl sulfate and fatty acid soaps of mono- and triethanolamine can also be used in shampoos and bubble bath formulations. Chemistry similar to that used in soluble oils and other emulsifiers is applicable to cleansing creams and lotions (102,103). Alkanolamides or salts are added to the shampoo base to give a smooth, dense foam (104).

Detergents. Alkanolamines, alkanolamine fatty acid soaps, and alkanolamides, with their mild alkalinity and excellent detergency characteristics, are used extensively in soaps and detergents. An alkanolamine salt of LAS (linear alkylbenzene sulfonate) forms the anionic surfactant component of many liquid laundry detergents (105). Monoalkanolamides have very limited water solubility and excellent alkaline resistance, resulting in widespread use in heavy-duty powder detergents as foam stabilizers and rinse improvers (106). Dialkanolamides are used in light-duty liquid detergents, where high alkalinity is not needed and high solubility is required.

The new liquid laundry detergents, with no phosphates, have developed a use for alkanolamines. In nonenzyme formulations, they contribute alkalinity, pH control, and enhanced product stability. In enzyme products, alkanolamines contribute to the stability of the enzyme in water solutions (107).

Electroplating, Electroless Plating and Stripping. Alkanolamines form complexes with many metal ions, and are consequently useful in electrolytic and chemical plating to improve coating properties. Diethanolamine is used in baths for electroplating palladium (108), triethanolamine in electroless baths for coating copper (109), and monoethanolamine in electrodeposition baths for zinc (110). Various coating formulations also contain alkanolamines, such as diethanolamine in cationic electrophoretic coatings (111), monoethanolamine in photoresist developers (112), and triethanolamine in formulations to protect electric switches and contact elements (113).

Alkanolamines are also used in formulations for removing photoresists (114,115) and cleaning printed-circuit boards (116). Formulations containing diethanolamine are used for electrodeposit coating of substrates (117).

Various documents relate to the use of formulations containing triethanolamine as flux for a variety of metals (118,119), for solders (120), for soldering pastes (121,122), and for low corrosion solder pastes (123).

Gas Purification. In the "sweetening" of natural gas, aqueous ethanolamine reacts with the hydrogen sulfide, carbon dioxide, or other acid constituents of the gas to give a water-soluble salt. The amine is then regenerated by steam stripping. Generally, monoethanolamine is used because of its low equivalent weight. Diethanolamine must be used, however, if there is a significant quantity of carbonyl sulfide in the gas, since this forms an unregenerable complex with monoethanolamine. The advantages of diethanolamine and monoethanolamine in treating refinery gases include low vapor pressure and hydrocarbon solubility (124).

Work continues on improving the efficiency of this process, such as for freeing the alkanolamine from heat-stable salts that can form (125). Formulations have been developed which inhibit degradation of mono- and diethanolamine in processing (126). Models (127), computer programs (128), and kinetics and enthalpies (129–136) have been developed to help determine equilibria of the acid gas–alkanolamine–water system. Additional references relate to the use of tertiary alkanolamines, such as triethanolamine, for gas conditioning (137–139).

Extensive work has been done on corrosion inhibitors (140), activated carbon use (141–144), multiple absorption zones and packed columns (145,146), and selective absorption and desorption of gas components (147,148). Alkanolamines can also be used for acid gas removal in ammonia plants (149).

Methyldiethanolamine (MDEA) and solutions of MDEA have increased in use for gas treating (150,151). Additional gas treating capacity can often be obtained with the same working equipment, because of the higher amine concentrations that can be used.

The Sulfinol gas conditioning process of Shell uses diisopropanolamine in a sulfolane solvent system. This system also increases gas capacity with improved efficiencies (152).

Metal Working, Cleaning, and Lubricating. Alkanolamines find wide use in the metal working industry, in formulations used for cutting fluids, lubricating oils, and cleaning solutions. The literature cites diethanolamine and triethanolamine as contributing biostatic effectiveness and high corrosion resistance (153). Triethanolamine derivatives, reacted with fatty acids, are formulated in emulsifiable oils, cutting fluids, and water-soluble cutting fluids (154–157). Triethanolamine is an excellent chelating agent in basic solutions. This chelating ability makes triethanolamine particularly useful in metal cleaning (158,159). Lubricants and coolants containing triethanolamine can increase the life of the cutting tool (160), increase the efficiency of the process (161), reduce surface roughness of the cutting tool (162), and reduce bactericidal concentrations (163).

Mining. Numerous patents have advocated the use of alkanolamines in mining applications. Triethanolamine has been used as a depressant in the flotation of copper (164), in the electrowinning of gold (165), and as an aid in the froth flotation of nickel ores. Phosphate ore flotation has been improved through the use of a fatty acid condensate with ethanolamine (166). Beneficiation of tin ore has been accomplished using fatty acid alkanolamides (167).

Petroleum and Coal. The alkanolamines have found wide use in the petroleum industry. The ethanolamines are used as lubricants and stabilizers in drilling muds. Reaction products of the ethanolamines and fatty acids are used as emulsion stabilizers, chemical washes, and bore cleaners (168). Oil recovery has been enhanced through the use of ethanolamine petroleum sulfonates (169–174). Oil–water emulsions pumped from wells have been demulsified through the addition of triethanolamine derivatives. Alkanolamines have been used in recovering coal in aqueous slurries and as coal–oil mix stabilizers (175–177).

Polymers. Because of their polyfunctionality, alkanolamines are used as additives in polyurethanes, polycarbonates, epoxy resins, polyesters, and other various resins and rubbers. Triethanolamine and triisopropanolamine are cited in the literature as cross-linking agents and curing agents in injection-molding formulations, contributing stability, strength, good impact, heat, and flame resistance (178–182) for urethanes. In polyester formulations, triethanolamine-based formulations give good physical and mechanical properties (183), form good coatings for concrete floors (184), and decrease molding pressure (185).

Monoethanolamine-containing formulations can be used to make polycarbonate molds with good dyeability and crack resistance (186). Monoethanolamine, diethanolamine, and triethanolamine have been cited in formulations for epoxy resins compounds (187–192).

Triisopropanolamine is used in natural rubber cross-linking and as a color stabilizer for polyethylene formulations. Chain termination of polybutadiene with triisopropanolamine gives improved cold-flow properties.

Alkanolamines can also be used to improve thermal stability in PVC copolymers and polystyrene.

Textiles. Alkanolamines are used in many stages in the production of textiles, from fiber manufacture, fiber lubrication, and fabric bleaching to fiber dyeing, and finishing. The alkanolamine fatty acid soaps and salts are used to lend antistatic properties to the fibers (193–195). Soluble oils can be formulated for easy removal from the fabric. Fabric lubrication can be accomplished with alkanolamine derivatives or alkanolamine-containing formulations (196,197). Ethanolamines can improve dyeing in a number of fabrics, including cotton (198), triacetate textiles (199), polyester-cellulosic fibers (200), acrylic fibers (201), polycarbonates (202), and leather (203). Quarternary alkanolamines can improve the dye stability (204), and act as fabric softeners as part of a formulation (205,206). Treatment of wool with a dilute solution of monoethanolamine, followed by steaming, imparts a durable crease (207) and sizing (208).

Pigment Dispersion. The alkanolamines and their derivatives are useful in dispersing titanium dioxide and other pigments (209). Monoisopropanolamine and triethanolamine are particularly effective in aiding titanium dioxide dispersion in the production of TiO₂ and in water-based paints (210). The alkanolamines are also an aid in the grinding of titanium dioxide (211).

Wood Pulping. Numerous patents have appeared in recent years regarding the use of alkanolamines in wood pulping. Pretreatment of wood chips with monoethanolamine has resulted in increasing yields from the alkaline pulping process (212). Monoethanolamine has also been used as an aid to increase pulp (qv) strength and brightness (213). Monoethanolamine has been used to impregnate wood to a more dense configuration (214). Combinations of an aqueous lignin slurry with monoethanolamine have produced a lignin salt that is suitable for printing compositions (215).

Chemical Processing Intermediates and Other Applications. Monoethanolamine can be used as a raw material to produce ethylenediamine. This technology has some advantages over the ethylene dichloride process in that salts are not a by-product. Additional reactions are required to produce the higher ethyleneamines that are normally produced in the ethylene dichloride process.

Alkanolamines are used in the manufacture of a variety of pharmaceutical compounds. Some of these products include antitumor agents, anti-inflammatory and allergy agents, and anticonvulsants. The literature reports ethanolamine derivatives in the treatment of Alzheimer's disease (216), the treatment of cerebral psychoorganic syndromes (217), and veterinary drugs (218).

The major use of alkanolamines in agricultural products is as a neutralizer for acidic herbicides. They also contribute increased water solubility, reduced volatility, and more uniform solutions. Various ethanolamines are reported in formulations to improve potato tuber size (219) and enhance the resistance to salt of some crops (220).

A variety of applications, including photography, employ alkanolamines for pH control. Reports have described formulations including monoethanolamine and triethanolamine in films and processing (221–224).

Diethanolamine can be used in the manufacture of morpholine (eq. 7).

Alkylalkanolamines. Aminoethylethanolamine and its derivatives are used in textiles, detergents, fabric softeners, chelating agents, water treating, petroleum, oil field and gas conditioning products, agricultural and pharmaceutical products, emulsifiers, mining chemicals, corrosion inhibitors, and surfactants for cosmetics (225).

Dimethylethanolamine, diethylethanolamine, and their derivatives are used in pesticides, corrosion inhibitors, drugs and pharmaceuticals, emulsification, paints and coatings, metal fabrication and finishing, petroleum and petroleum products, and plastics and resins (226).

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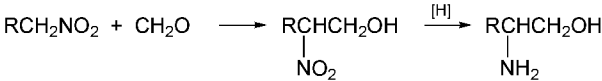
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ALKANOLAMINES FROM NITRO ALCOHOLS

The nitro alcohols (qv) obtained by the condensation of nitroparaffins (qv) with formaldehyde [50-00-0] may be reduced to a unique series of alkanolamines (β-amino alcohols):



The condensation may occur one to three times, depending on the number of hydrogen atoms on the α-carbon of the nitroparaffin, giving rise to amino alcohols with one to three hydroxyl groups. A comprehensive review of these compounds has been published (1).

Many members of this series are known based on nitroparaffin condensations with aldehydes of longer chain length than formaldehyde. However, only the five primary amino alcohols discussed in the following are manufactured on a commercially significant scale. N-Substituted derivatives of these compounds also have been prepared, but only 2-dimethylamino-2-methyl-1-propanol has been available in commercial quantities (Table 1).

Table 1. Commercial Alkanolamines

Name	Common designation	Molecular formula	CAS Registry Number	Molecular weight
2-amino-2-methyl- 1-propanol	AMP	C ₄ H ₁₁ NO	[124-68-5]	89.14
2-amino-2-ethyl-1,3-propanediol	AEPD ^a	C ₅ H ₁₃ NO ₂	[115-70-8]	119.16
2-dimethylamino-2-methyl-1-propanol	DMAMP	C ₇ H ₁₅ NO	[7005-47-2]	117.19
2-amino-2-(hydroxymethyl)- 1,3-propanediol ^b	TRIS AMINO ^a	C ₄ H ₁₁ NO ₃	[77-86-1]	121.14
2-amino-2-methyl- 1,3-propanediol	AMPD	C ₄ H ₁₁ NO ₂	[115-69-5]	105.16
2-amino-1-butanol	AB ^a	C ₄ H ₁₁ NO	[96-20-8]	89.14

^a AB, AEFD and TRIS AMINO are registered trademarks of ANGUS Chemical Company.

^b Common name is tris(hydroxymethyl)aminomethane.

Physical Properties

Physical properties of the six commercial alkanolamines are given in Table 2. Because 2-amino-2-methyl-1-propanol (AMP) and 2-amino-2-ethyl-1,3-propanediol (AEPD) melt near room temperature and usually contain some water, they may be semisolid pastes, rather than crystalline solids. Water-diluted forms of both these alkanolamines are marketed because such solutions remain liquid at lower temperatures than do the pure compounds, eg, AMP-95, which contains 5% water, solidifies at -2°C.

Table 2. Properties of Alkanolamines

Compound	Boiling point, °C	Melting point, °C	Specific gravity	pH of 0.1 M aqueous solution	pK _a at 20°C
AMP	165 ^a	30–31	0.934 ^b	11.3	9.82
AEPD	152–153 ^c	37.5–38.5	1.099 ^b	10.8	8.80
DMAMP	160 ^a	19	0.90 ^d	11.6	10.2
TRIS AMINO	219–220 ^c	171–172		10.4	8.03
AMPD	151–152 ^c	109–111		10.8	8.76
AB		2	0.944 ^b	11.1	9.52

^a At 101.3 kPa (1 atm).

^b At 20-25°C.

^c At 1.3 kPa (10 mm Hg).

^d At 25-25°C.

These compounds are highly soluble in water. AMP, AMPD, AEPD, and DMAMP are completely miscible in water at 20°C; the solubility of AB is 250 g/100 mL H₂O at 20°C. They are generally very soluble in alcohols, slightly soluble in aromatic hydrocarbons, and nearly insoluble in aliphatic hydrocarbons; tris(hydroxymethyl)aminomethane [77-86-1] is appreciably soluble only in water (80 g/100 mL at 20°C) and methanol.

Alkanolamines have high boiling points and under normal ambient conditions their vapor pressures are low. Only DMAMP (see Table 2) forms an azeotrope with water, which boils at 98.4°C and contains 25% by weight of DMAMP. According to current DOT regulations, AMP, AMP-95, DMAMP, DMAMP-80, AEPD, and AB are all classified as combustible liquids.

DMAMP and AMP are among the strongest amines commercially available. The dissociation constants of these materials appear in Table 2. All alkanolamines have slight amine odors in the liquid state; the solids are nearly odorless.

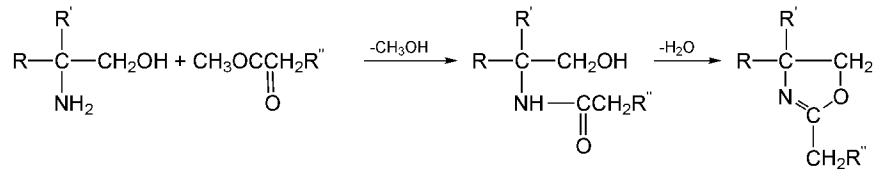
Chemical Properties

The alkanolamines discussed here exhibit the chemical reactivity of both amines and alcohols, as is the case with other alkanolamines. Typically, they attack copper, brass, and aluminum, but not steel or iron. Alkanolamines are useful as amination agents; however, the reactivity of both the amino and alcohol

group must be considered in attempting any specific synthetic scheme.

With mineral acids, the alkanolamines form ammonium salts which hydrolyze readily in the presence of water and dissociate on heating. Fatty acids, such as oleic, give soaps which are highly efficient emulsifying agents with important industrial uses, particularly the soaps of AMP (see EMULSIONS; SURFACTANTS).

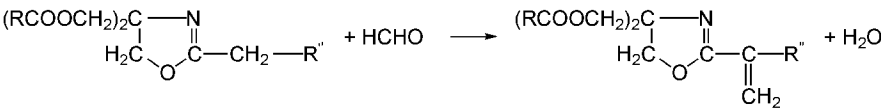
On heating, an alkanolamine soap first dehydrates to the amide; this is also obtained from the methyl ester of the fatty acid by heating with the alkanolamine at 60°C in the presence of a catalytic amount of sodium methoxide. Methanol is removed under partial vacuum. At higher temperature, the amide is dehydrated to an oxazoline.



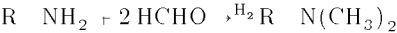
where for AEPD, R = C₂H₅, R' = CH₂OH and for TRIS AMINO, R = R' = CH₂OH

These oxazolines have cationic surface-active properties and are emulsifying agents of the water-in-oil type. They are acid acceptors and, in some cases, corrosion inhibitors (see CORROSION). Reaction to oxazoline also is useful as a tool for determination of double-bond location in fatty acids (2), or for use as a protective group in synthesis (3). The oxazolines from AEPD and TRIS AMINO contain hydroxyl groups that can be esterified easily, giving waxes (qv) with saturated acids and drying oils (qv) with unsaturated acids.

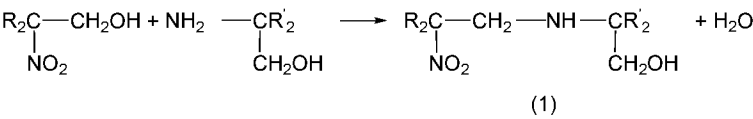
Formaldehyde reacts with the hydrogen on the α-carbon of the fatty acid from which the oxazoline was formed to yield a vinyl monomer which can be polymerized or utilized for synthesis (4). Thus, esters of the oxazoline formed from TRIS AMINO undergo the reaction



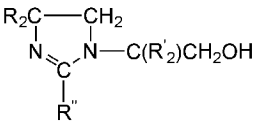
These products are useful for modification of alkyd resins (qv), preparation of paint vehicles, and copolymerization with other monomers. Substitution on the amino group occurs readily, giving bases stronger than the parent amines.



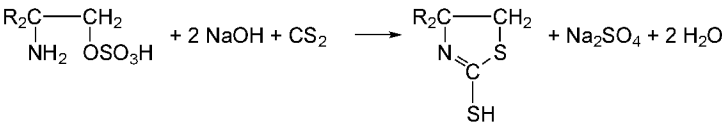
Alkanolamines react with nitro alcohols to form nitrohydroxylamines (5).



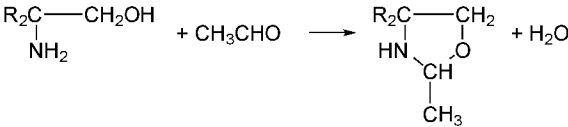
Some of these compounds show antibacterial activity. Reduction gives 2-[(2-aminoethyl)amino]ethanols which react with organic acids to form amides that, on further heating, cyclize to imidazolines (6). For example, the diamine obtained by reducing (1) reacts with an organic acid (R''COOH) to give



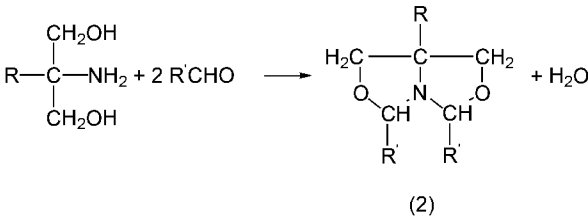
Mercaptothiazolines are obtained from the corresponding sulfate esters and carbon disulfide.



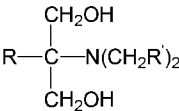
Aldehydes react with monohydric alkanolamines to give monocyclic oxazolidines



or with polyhydric alkanolamines to give bicyclic oxazolidines (7,8)



These can be hydrogenated to N,N-substituted alkanolamines. Thus (2) yields



Oxidation of the hydroxyl group, after protection of the amine group by benzylation, gives amino acids (7), eg, oxidation of 2-amino-2-methyl-1-propanol to 2-methylalanine [62-57-7], (CH₃)₂CNH₂COOH.

Manufacture and Economic Aspects

The reduction of nitro alcohols to alkanolamines is readily accomplished by hydrogenation in the presence of Raney nickel catalyst (1,9,10). AMP, AEPD, and AB are purified by distillation. TRIS AMINO and AMPD are purified by crystallization. TRIS AMINO concentrate in water (40° assay) is also available.

2-Dimethylamino-2-methyl-1-propanol is manufactured from AMP by hydrogenation in the presence of formaldehyde and purified by distillation. It is marketed primarily as DMAMP-80 (water added), however.

Production statistics on alkanolamines are not available, but they are sold in thousand-ton quantities and are available for bulk shipment except for DMAMP, AB, TRIS AMINO, and AMPD (the latter two being crystalline solids). TRIS AMINO concentrate is available in bulk. AMPD is manufactured only in low volumes to meet limited demand in certain specialized uses. Similarly, 2-AB is manufactured only to meet demand for one end use.

ANGUS Chemical Company is the only basic manufacturer of technical-grade TRIS AMINO (Tromethamine). However, ANGUS and numerous processors offer recrystallized, high purity grades of this alkanolamine for biomedical applications.

Table 3 gives the 1990 prices for bulk quantities and the net weights packaged in drums or bags; Table 4 gives the specifications.

Table 3. 1990 U.S. Prices of Alkanolamines, \$/kg

Product	Tank car	Carload	Net weight, kg ^a
AMP	5.28	5.41	191.6 (D)
AMP-95	2.55	2.68	191.6 (D)
AEPD		3.19	204.5 (D)
AEPD-85	1.85	1.96	204.5 (D)
TRIS AMINO crystals		11.99	22.7 (B)
TRIS AMINO 40° aqueous	3.08	3.21	226.9 (D)
TRIS AMINO ultrapure		18.50	50 (F)
DMAMP-80		13.20	186 (D)
AMPD		88.00	11.3,22.6 (F)
AB		^b	193.2 (D)

^a D 28 L (55-gal) steel drums; B bags; F fiber drums.

^b Price available only by quotation.

Table 4. Specifications for Alkanolamines

Product	Neutral equivalent	Color, APHA, max	Water, wt % ^o , max	Melting point, °C, min	Amine assay, % ^o
AMP	88.5–91.0	20	0.8		
AMP-95	93.0–97.0	20	4.8–5.8		
AEPD	124.0, max	2 ^{a,b}	3.8		
AEPD-85		2 ^{a,b}	13.0–15.0		
DMAMP-80		100	18.0–22.0		78.0–82.0 ^d
AMPD ^c	103.0–107.0	50 ^d	0.5	100.0	
AB		100	0.5		98.0
TRIS AMINO 40° aqueous		5 ^a			38.0–42.0 ^d
crystals	121.0–122.0	40 ^d	0.5	160.0	
ultrapure ^{e,f}		20 ^d	0.2	170.0–172.0	99.9–100.1

^a Gardner color.

^b 20° aqueous solution.

^d By titration.

^c Residue on ignition 0.01 wt%, max; insoluble matter 0.01 wt%, max.

^e Addition specifications for heavy metal content; meets USP and ACS specifications.

^f Residue on ignition 0.05 wt%, max; insoluble matter 0.005 wt%, max.

Health and Safety Factors

Alkanolamines are only slightly toxic by ingestion (acute oral LD₅₀ in rodents 1.0–5.5 g/kg).

Undiluted DMAMP, AMP-95, and AB cause eye burns and permanent damage, if not washed out immediately. They are also severely irritating to the skin, causing burns by prolonged or repeated contact. Of these three alkanolamines, only AMP has been studied in subchronic and chronic oral studies. The principal effect noted was the action of AMP on the stomach as a result of its alkalinity. The no-observed-effect level (NOEL) in a one-year feeding study in dogs was 110 ppm in the diet. In general, the low volatility and applications for which these products are used preclude the likelihood of exposure by inhalation.

AEPD is severely irritating to the eyes and should be washed out immediately on contact; it is only mildly irritating to the skin.

AMPD and TRIS AMINO, normally crystalline solids, are of less concern in terms of irritancy to skin and eyes.

The 40° aqueous solution of TRIS AMINO is nonirritating to the eyes and skin. In general, the toxicology of the alkanolamines is typical of alkaline materials, ie, the greater the base strength, the greater the effect. Neutralized alkanolamines are much less toxic; their stearate soaps, for instance, have been found to be nonhazardous.

TRIS AMINO, the least toxic of this series of alkanolamines, has been studied extensively (11). It is used in a number of pharmaceutical applications and has been used intravenously as a buffering agent for control of acidosis.

Environmentally, these alkanolamines present little problem. Only AMP has been studied extensively, but it was found to be degradable, to be of low toxicity to fish and microorganisms, and to be nonaccumulative. TRIS AMINO has been added to water used to ship fish in order to improve viability.

Uses

Because they are similar, the alkanolamines often can be used interchangeably. However, cost performance considerations generally dictate a best choice for specific applications. AMPD is manufactured in very low volumes for use as a reagent in certain medical diagnostic tests, although some is used in certain cosmetic products. 2-Amino-1-butanol is used primarily as a raw material for the synthesis of ethambutol [74-55-5], an antituberculosis drug. The first step in the synthesis of this drug is the resolution of AB into its optical isomers because only (*S*)-2-amino-1-butanol, [5856-62-2] is utilized in this synthesis.

Emulsions. The fatty acid soaps of alkanolamines are excellent emulsification agents for use in such products as floor polishes, cosmetics, and functional fluids such as hydraulic and metalworking fluids. For example, improved hardwater stability of a hydraulic fluid emulsion is obtained using AMP in the formulation (12).

Pigment Dispersion. AMP is used widely as a pigment dispersant for water-based paints and paper coatings. In small amounts, it efficiently disperses pigments and improves pH stability, viscosity, corrosion inhibition, and odor (13). When AMP is used in conjunction with other surfactants, enhanced performance is obtained with less of these ingredients in the dispersion.

TiO₂ and clay slurries which utilize AMP as part of the dispersant system are available in bulk for the paint and paper industries (see PIGMENTS). More recently, AMP has been used as a surface treatment for production of TiO₂ with improved luster and dispersibility (14).

Resin Solubilizers. In general, water-soluble resins are amine salts of acidic polymers. Water-soluble coatings formulated with AMP-95 and DMAMP-80 exhibit superior performance (15,16) (see WATER SOLUBLE POLYMERS). AMP-95, used in conjunction with associative thickeners (17) or hydroxy-ethylcellulose, provides for the most efficient utilization of such thickeners. It also is the neutralizer of choice for use with hair spray resins.

Catalysts. The alkanolamines continue to find use as blocked catalysts for textile resins, coatings resins, adhesives, etc. Of particular utility in curing durable-press textiles is AMP·HCl. Other salts, such as those of the benzoin tosylate or *p*-toluenesulfonic acid, find utility in melamine- or urea-based coatings (18) (see AMINO RESINS AND PLASTICS).

Boiler Water Treatment. Alkanolamines, in general, provide excellent corrosion protection to steel in many applications. When used in boiler water treatment, AMP provides excellent protection to steel and copper in steam lines through efficient absorption of CO₂, effectual distribution ratio for transport throughout the system, and minimum amine loss in the deaerating heater (19–21).

Formaldehyde Scavenging. The formation of oxazolidines from alkanolamines and formaldehyde is rapid at room temperature and provides a method for the elimination of excess formaldehyde from products such as urea–formaldehyde resins. AEPD and TRIS AMINO are the products of choice for this purpose because one mole of each will react with two moles of formaldehyde (22).

Applications in Oil and Gas Production. AMP is useful for removing CO₂ from gaseous mixtures (23). It also has been utilized in tertiary oil recovery to enhance removal of petroleum from marginal wells (24).

Biomedical Applications. TRIS AMINO is used for a number of purposes: in its pure form, it is an acidimetric standard; the USP grade can be utilized intravenously for therapeutic control of blood acidosis; TRIS AMINO also is useful in genetic engineering as a buffering agent for enzyme systems, industrial protein purification, and electrophoresis. AMP has found use as a reagent in enzyme-linked immunoassays. The primary application is for alkaline phosphatase assays.

Synthetic Applications. Oxazolines, which are synthesized as indicated above, have been utilized in many different applications (25). When used in resin formulations, AMP, AEPD, and TRIS AMINO can incorporate the oxazoline structure into the polymer structure (26). Because they are polyols, both AEPD and TRIS AMINO can be used in polyester resin modification. Oxazoline alkyd films are characterized by improved performance, particularly salt-spray resistance and gloss (see ALKYD RESINS; COATINGS, SPECIAL PURPOSE, HIGH PERFORMANCE).

Other oxazolines synthesized from alkanolamines are useful as surface-active agents and corrosion inhibitors. Synthetic oxazoline waxes promote lubricity and mar resistance of coatings.

Oxazolidines, formed by reaction of alkanolamines with aldehydes, are useful as leather tanning agents and are effective curing agents for proteins, phenolic resins, moisture-cure urethanes, etc. They also find use as antimicrobial agents.

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ALKOXIDES, METAL

Metal alkoxides are compounds in which a metal is attached to one or more alkyl groups by an oxygen atom. Alkoxides are derived from alcohols by the replacement of the hydroxyl hydrogen by metal.

Sodium ethoxide was the first metal alkoxide described in 1837 (1). The alkoxides of many transition metals were developed after World War II (2–5). Today some alkoxides, including those of sodium, potassium, magnesium, aluminum, zirconium, and titanium, are commercially important. The name metal alkoxides is preferred, although metal alcoholates is also used.

Alkoxides of nonmetals are described in articles about the corresponding compounds (see BORON COMPOUNDS, BORON OXIDES; SILICON COMPOUNDS). Metal alkyls, in which the alkyl group is bound directly to the metal, are also discussed elsewhere (see ALUMINUM COMPOUNDS).

Physical Properties

The metal alkoxides exhibit great differences in physical properties (Tables 1 and 2), depending primarily on the position of the metal in the periodic table, and secondarily on the alkyl group. Many alkoxides are strongly associated by intermolecular forces (3,49,50) which depend on the size and shape of the alkyl groups. This explains the fact that many metal methoxides are solid, nondistillable compounds, because the small methyl group has little screening effect on the metal atom. With a larger number of methyl groups and a smaller atomic radius of the metal, methoxides become sublimable and even distillable.

Table 1. Physical Properties of Metal Ethoxides^a

Alkoxide	CAS Registry Number	Color and physical form	mp, °C	bp, °C	P _a ^b	Solubility in organic solvents	References
LiOC ₂ H ₅	[2388-07-0]	white solid	20–24	n.d. ^c		+	6,8
NaOC ₂ H ₅	[141-52-6]	white solid	260 (dec)	n.d.		+	6,8
KOC ₂ H ₅	[917-58-8]	white solid	250 (dec)	n.d.		+	6,8
TiOC ₂ H ₅	[20398-06-5]	colorless liquid	9.5	n.d.		+	6,9
Mg(OC ₂ H ₅) ₂	[22005-12-5]	white solid	270 (dec)	n.d.		(+) ^d	6,10
Ca(OC ₂ H ₅) ₂	[2914-17-2]	white solid	270 (dec)	n.d.		+	6,9
Sr(OC ₂ H ₅) ₂	[2914-18-3]	white solid	300 (dec)	n.d.		+	6,9
Ba(OC ₂ H ₅) ₂	[2914-19-4]	white solid	270 (dec)	n.d.		+	6,9
Zn(OC ₂ H ₅) ₂	[3851-22-7]	white solid					11,12
Sn(OC ₂ H ₅) ₂	[14791-99-2]	white solid	200 (dec)			(+)	13
Mn(OC ₂ H ₅) ₂	[52321-91-2]	dark-brown solid				(+)	14
Al(OC ₂ H ₅) ₃	[555-75-9]	white solid	140	189	400	+	6,15
Ga(OC ₂ H ₅) ₃	[2572-25-0]	white solid	144.5	180–190	150 ^e	+	16,17
Cr(OC ₂ H ₅) ₃	[7245-26-3]	light-green solid				(+)	18
Fe(OC ₂ H ₅) ₃	[5058-42-4]	dark-brown solid	120	155	10	+	19,20
Sb(OC ₂ H ₅) ₃	[10433-06-4]	colorless liquid		37–38	5	+	21,22
VO(OC ₂ H ₅) ₃	[1686-22-2]	almost colorless liquid	ca 8	91	1100	+	22,23
Ti(OC ₂ H ₅) ₄	[3087-36-3]	white solid	ca 40	124	160	+	24,25
Zr(OC ₂ H ₅) ₄	[18267-08-8]	white solid	172	180	13	+	26,27
Hf(OC ₂ H ₅) ₄	[13428-80-3]	white solid	ca 180	180–200	13	(+)	28
Th(OC ₂ H ₅) ₄	[64653-68-5]	white solid	300 (dec)			(+)	29
Ce(OC ₂ H ₅) ₄	[64653-69-6]	yellow solid	200 (dec)				30
V(OC ₂ H ₅) ₄	[7637-16-3]	brown solid		100	5	+	31
Ge(OC ₂ H ₅) ₄	[14165-55-0]	colorless liquid	72	54.5	670	+	32,33
Sn(OC ₂ H ₅) ₄	[3173-69-1]	white solid	unmeltable		n.d.	+	34,35
U(OC ₂ H ₅) ₄	[64653-70-9]	light-green liquid	dec				36
Nb(OC ₂ H ₅) ₅	[3236-82-6]	light-yellow liquid	6	156	6.6	+	37
Ta(OC ₂ H ₅) ₅	[6074-84-6]	colorless liquid	22	137	6.6	+	37,38
W(OC ₂ H ₅) ₅	[26143-11-3]	red-black liquid		120	6.6	+	7
U(OC ₂ H ₅) ₅	[10405-34-2]	dark-brown liquid	180 (dec)	160	6.6	+	39,40
Sb(OC ₂ H ₅) ₅	[7610-33-5]	colorless solid	46	135–145	20	+	41
U(OC ₂ H ₅) ₆	[64653-71-0]	dark-red liquid		72	0.13	+	42

^a Refs. 6, 7.

^b To convert Pa to mm Hg, divide by 133.3.

^c n.d. = not distillable.

^d Less soluble.

^e Sublimes.

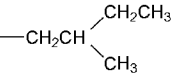
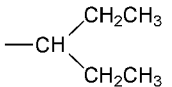
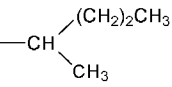
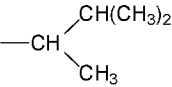
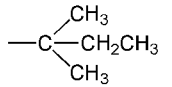
Table 2. Physical Properties of Double Alkoxides

Alkoxide ^a	CAS Registry Number	mp, °C	bp, °C Pa ^b	Reference ^c
K[Li(OC ₃ H ₇) ₂]	[64653-73-2]			44
Na[Zr ₂ (OC ₃ H ₇) ₉] ^d	[24492-19-1]	168–180	260 1	45
K[Zr ₂ (OC ₃ H ₇)] ^d	[64653-75-4]		subl 200 26.6	45
Li[Zr ₂ (OC ₃ H ₇) ₉]	[64653-74-3]		260 26.6	45
Tl[Zr ₂ (OC ₃ H ₇)]	[64683-25-6]		subl 220 66.5	45
Mg[Al(OC ₂ H ₅) ₄] ₂	[64653-77-6]	129	220–228 53.5	44
Ca[Al(OC ₃ H ₇) ₄] ₂	[64653-61-8]	124	230–240 400	44
K[Al(OC ₄ H ₉) ₄]	[64653-62-9]	164–165		44
Mg[Al(OC ₃ H ₇) ₄] ₂	[64653-63-0]	20	130–142 260	44
Co[Al(OC ₂ H ₅) ₄] ₂ ^{d,e}	[64653-64-1]			44
Na[Sn ₂ (OC ₂ H ₅) ₉] ^d	[24992-46-1]	260 (dec)		44
Ca[U(OC ₂ H ₅)] ₂ ^f	[64653-65-2]		subl 200 0.13	46
Al[U(OC ₂ H ₅)] ₃ ^{d,g}	[64653-66-3]		111–115 0.16	47
U[Al(OC ₃ H ₇) ₄] ₄ ^{d,h}	[64653-67-4]		95–97 0.13	48
Na[U(OC ₂ H ₅)] ^f	[64653-58-3]	dec		47

^a White solids unless otherwise noted.
^b To convert Pa to mm Hg, divide by 133.3.
^c See references 11 and 43 for double alkoxides of zinc, aluminum, gallium, and indium, respectively.
^d Soluble in organic solvents.
^e Violet solid.
^f Green solid.
^g Green liquid.
^h Green oil.

Table 3 (3) shows the influence of branching of the alkyl group on volatility and complexity, using titanium and zirconium amyl oxides as examples.

Table 3. Boiling Points and Molecular Complexities of Amyloxides of Titanium and of Zirconium

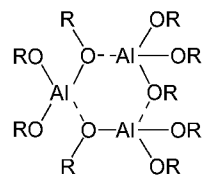
R in M(OR) ₄	Titanium alkoxide			Zirconium alkoxide		
	CAS Registry Number	bp, °C Pa ^a	Molecular complexity	CAS Registry Number	bp, °C Pa ^a	Molecular complexity
(CH ₂) ₄ CH ₃	[1058-24-1]	175 80	1.4	[64653-49-2]	256 1	3.2
(CH ₂) ₂ CH(CH ₃) ₂	[19480-47-8]	148 10	1.2	[64653-50-5]	247 10	3.3
	[64653-51-6]	154 50	1.1	[64653-52-7]	238 10	3.7
CH ₂ C(CH ₃) ₃	[35061-92-8]	105 5	1.3	[26159-00-2]	188 20	2.4
	[64653-53-8]	112 5	1.0	[64653-54-9]	178 5	2.0
	[53973-00-5]	135 100	1.0	[64653-55-0]	175 5	2.0
	[64653-56-1]	131 50	1.0	[64653-57-2]	156 1	2.0
	[10585-26-9]	98 10	1.0	[24675-20-5]	95 10	1.0

^a To convert Pa to mm Hg, divide by 133.3.

Many metal alkoxides are soluble in the corresponding alcohols, but magnesium alkoxides are practically insoluble. Only the distillable alkoxides, like those of aluminum, titanium, and zirconium, are soluble in weakly polar solvents. The double alkoxides are soluble in alcohol; K[Li(OC₃H₇)₂], Tl[Zr₂(OC₃H₇)₉], and Na[Sn₂(OC₂H₅)₉] may be crystallized from alcohol. Li[Zr₂(OC₃H₇)₉] may be crystallized from benzene. Several are soluble in organic

solvents as indicated in Table 2; Na[U(OC₂H₅)] is only slightly soluble.

Much work has been done on the structure of the metal alkoxides (49). The simple alkali alkoxides have an ionic lattice and a layer structure, but alkaline earth alkoxides show more covalent character. The aluminum alkoxides have been thoroughly studied and there is no doubt as to their covalent nature; the lower alkoxides are associated, even in solution and in the vapor phase. The degree of association depends on the bulkiness of the alkoxy group and can range from 2 to 4, eg, the freshly distilled isopropylate is trimeric (4):



Structures are highly varied among the transition metals. The titanium atom in titanium tetraethoxide has the coordination number 6 (Fig. 1). The corresponding zirconium compound, with coordination number 8, has a different structure (Fig. 2). Metal alkoxides are colored when the corresponding metal ions are colored, otherwise they are not.

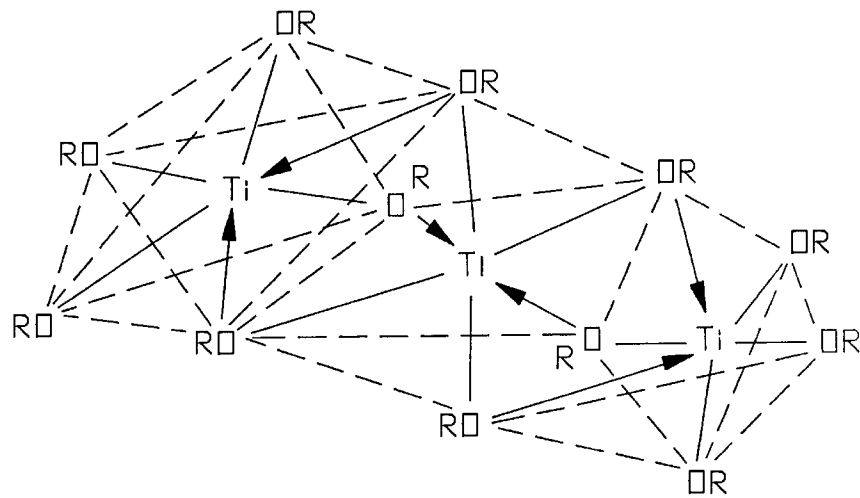


Fig. 1. Structure of Ti₃(OR)₁₂.

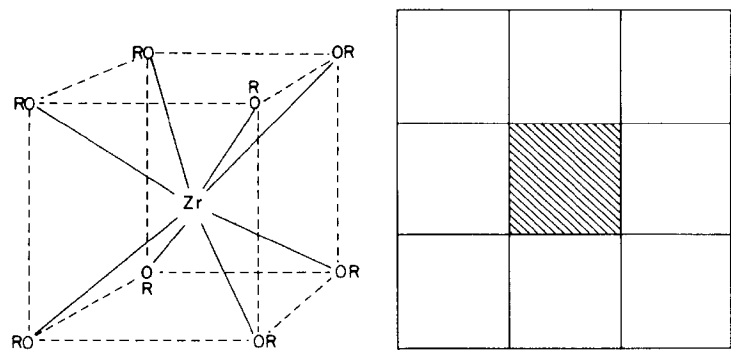
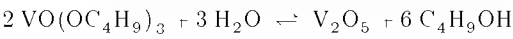
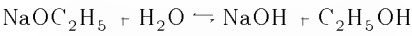


Fig. 2. Structure of Zr(OR)₈. Left, unit A; right, plane view, eight of unit A.

Chemical Properties

The most outstanding property of the metal alkoxides is ease of hydrolysis.



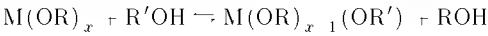
This is used for sol-gel applications (51–54), a three step process:

- (1) Partial hydrolysis of a metal alkoxide to form reactive monomers.
- (2) Condensation of these monomers to form colloidlike oligomers (sol formation).
- (3) Additional hydrolysis to promote polymerization and cross-linking leading to a three-dimensional matrix and gel formation.

Although outlined here in a sequential fashion, these reactions occur simultaneously at various stages of the overall process.

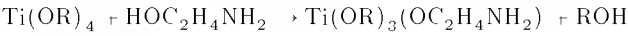
Uranium hexa-*tert*-butoxide is an exception and does not react with water (55). References 3 and 5 discuss chemical properties of alkoxides. In some cases hydrolysis is reversible, but usually it is not (23,56).

The reaction of alkoxides with alcohols leads to the equilibrium

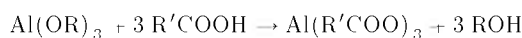


Dihydric alcohols give normal or cyclic alkoxides.

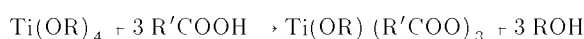
Amino alcohols react similarly (57):



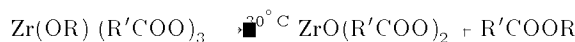
Metal alkoxides and carboxylic acids give salts (58):



Titanium tetraalkoxides react with only three equivalents of acid (59):



In some cases the mixed salts are unstable and eliminate an ester (60):



Metal alkoxides and phenol usually form phenolates smoothly (61).

Enols and alkoxides give chelates with elimination of alcohol. For example, in the reaction of the enol form of acetylacetone [123-54-6] all four alkoxide groups attached to zirconium can be replaced, but only two of the four attached to titanium (Fig. 3). Acetoacetic esters react similarly.

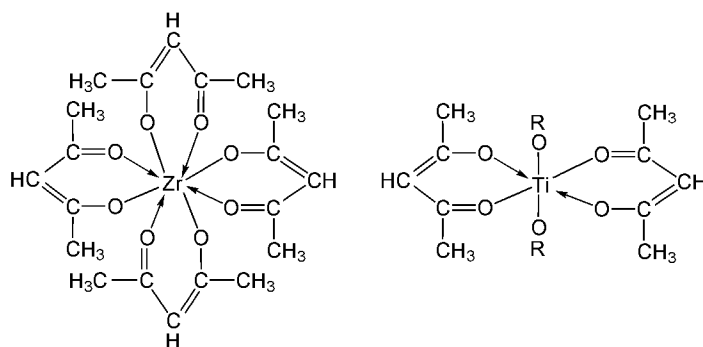
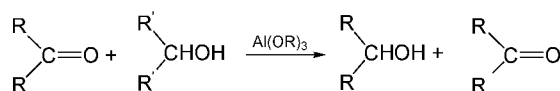
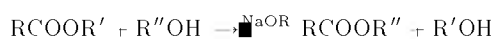
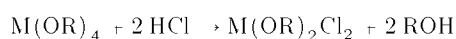
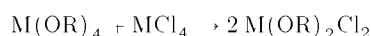
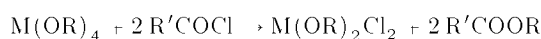


Fig. 3. Products of the reaction of M(OR)_4 with $\text{CH}_3-\text{C}(\text{OH})=\text{CH}-\text{C}(=\text{O})-\text{CH}_3$ where $\text{M} = \text{Zr}$, coordination number 8, or Ti , coordination number 6.

Metal alkoxides catalyze the Tishchenko condensation of aldehydes (62), the transesterification of carboxylic esters, the Meerwein-Ponndorf reaction (63), and other enolization and condensation reactions.

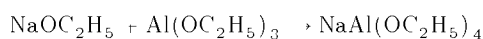


Mixed chloride alkoxides are prepared by reaction with acyl chlorides, metal chlorides, hydrogen chloride, or chlorine (64).

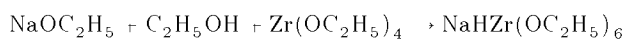


Bromine compounds are prepared similarly. These reactions are best carried out in an inert solvent.

Alkoxides often react to give double alkoxides (44):



In the presence of alcohol, another type of double alkoxide also forms (44):



Other double alkoxides are more covalent, distillable, and often more soluble in organic solvents.

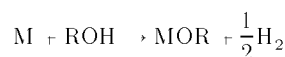
Alkaline earth metal alkoxides decompose to carbonates, olefins, hydrogen, and methane; calcium alkoxides give ketones (65). For aluminum alkoxides, thermal stability decreases as follows: primary > secondary > tertiary; the respective decomposition temperatures are ca 320°C, 250°C, and 140°C. Decomposition products are ethers, alcohols, and olefins.

Zirconium alkoxides behave similarly in regard to thermal stability. The series zirconium methoxide [28469-78-5], zirconium ethoxide [18267-08-8], zirconium isopropoxide [2171-98-4], zirconium *tert*-butoxide [2081-12-1] shows decreasing thermal stability.

Many metal alkoxides decompose at higher temperatures to lower valency compounds, in some cases to metal.

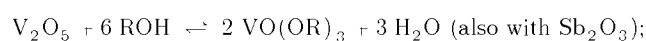
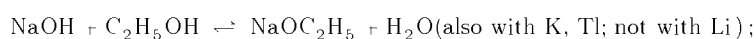
Preparation

From Metals and Alcohol. Alkali metals, alkaline earth metals, and aluminum react with alcohols to give metal alkoxides (2,3,65):



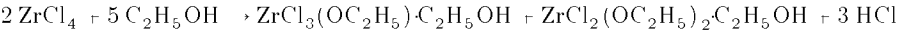
The speed of the reaction depends both on the metal and on the alcohol, increasing as electropositivity increases and decreasing with length and branching of the chain. Thus sodium reacts strongly with ethanol, but slowly with tertiary butyl alcohol. The reaction with alkali metals is sometimes carried out in ether, benzene, or xylene. Some processes use the metal amalgam or hydride instead of the free metal. Alkaline earth metals and aluminum are often covered with an oxide film which hinders the reaction.

From Metal Oxides and Hydroxides This reaction is usually an equilibrium in which the water must be removed by physical or chemical means (23,56,66):



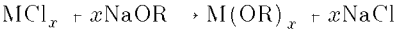


From Metal Halides. The reaction of metal chlorides with alcohols can give metal chloride alkoxides (67–69), eg

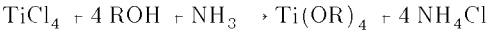


The HCl formed can lead to secondary reactions, especially with unsaturated or tertiary alcohols.

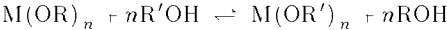
Metal alkoxides may achieve complete replacement of halogen.



Ammonia and alcohol may be used instead of sodium alkoxides to manufacture alkoxides of titanium and other metals such as zirconium, hafnium, germanium, niobium, tantalum, aluminum, and tin.



From Alcoholysis and Transesterification. Metal alkoxides of higher, unsaturated, or branched alcohols are difficult to prepare directly and are usually made from lower metal alkoxides by means of alcoholysis:

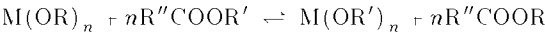


The reaction is driven to completion by distilling the lower boiling alcohol. Metal methoxides are frequently insoluble and cannot be employed as starting materials in this reaction; by the same token, they can be conveniently prepared from solutions of higher alkoxides by precipitation with methanol.

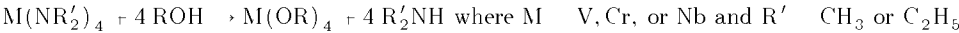
Alcoholysis also gives mixed metal alkoxides:



Transesterification with carboxylic acid esters is also useful (70):



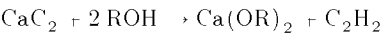
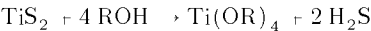
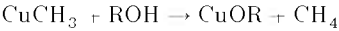
From Metal Amides. Dimethyl and diethyl amides of some metals react smoothly to give good yields of certain metal alkoxides that are otherwise difficult to obtain (71,72).



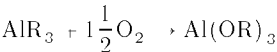
Mixed Halide Alkoxides. Metal chlorides, hydrogen chloride, and carboxylic acid chlorides convert metal alkoxides to metal chloride alkoxides.

Double Alkoxides. Complex double alkoxides are formed when a solution of an alkali or alkaline earth metal alkoxide is added to a solution of an alkoxide of aluminum, titanium, or zirconium and a series of such compounds have been prepared (44).

Other Methods Other methods have only specialized significance. These include alcoholysis of organometallic compounds (73), sulfides (74), and carbides (75),

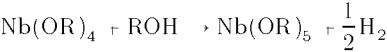
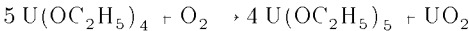
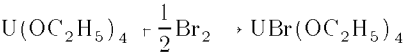


and oxidation of organometallic compounds (76):

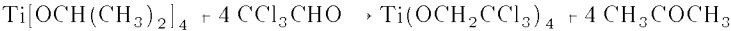


This reaction is important in the manufacture of long-chain alcohols by means of hydrolysis of the aluminum alkoxide.

Examples of oxidation of metal alkoxides (40,42) include:



The Meerwein-Ponndorf reaction may be exemplified by (77):



Commercial Alkoxides

Table 4 lists the manufacturers of some metal alkoxides, and the individual materials are described in the following. Some other properties of metal ethoxides are summarized in Table 1.

Table 4. Manufacturers of Metal Alkoxides

Product	Producer	Country
sodium methylate, solid	Amspec Chemical Corp.	USA
	Badische Anilin und Sodafabrik A.G.	Germany
	H&Ls A.G.	Germany
	Nippon Soda	Japan
	Olin Corp.	USA
solution	Amspec Chemical Corp.	USA
	Badische Anilin und Sodafabrik A.G.	Germany
	H&Ls A.G.	Germany
	Occidental Chemical Corp.	USA
	Olin Corp.	USA
sodium ethylate	Amspec Chemical Corp.	USA
	H&Ls A.G.	Germany

	Mitsubishi Chemical	Japan
	Nippon Soda	Japan
sodium <i>t</i> -butylate	Amspec Chemical Corp.	USA
	Callery Chemical Co. Div. of MSA	USA
sodium isopropylate	Amspec Chemical Corp.	USA
potassium methylate, solid	H&ls A.G.	Germany
potassium ethylate, solid	H&ls A.G.	Germany
potassium <i>t</i> -butylate, solid	H&ls A.G.	Germany
	Callery Chemical Co. Div. of MSA	USA
magnesium ethylate	H&ls A.G.	Germany
	Nippon Soda	Japan
	Mitsubishi Chemical	Japan
magnesium <i>n</i> -propylate	H&ls A.G.	Germany
magnesium alkoxides (other)	Specialty Organics Inc.	USA
	H&ls A.G.	Germany
calcium ethoxide	Mitsubishi Chemical	Japan
aluminum isopropylate	Chattem Chemical Co.	USA
	Deutsche Texaco A.G.	Germany
	Mitsubishi Chemical	Japan
	Nippon Soda	Japan
aluminum <i>sec</i> -butylate	Deutsche Texaco A.G.	Germany
aluminum alkoxides (other)	Ethyl Corp.	USA
	Hexcel Chemical Co.	USA
	Joseph Ayers	USA
	Nippon Soda	Japan
	Vista Chemical Co.	USA
titanium alkoxides	AKZO	USA
	Black Uhler Chemical Co., Inc.	USA
	E. I. du Pont de Nemours & Co., Inc.	USA
	H&ls A.G. H&ls America, Inc.	Germany USA
	Kenrich Petrochems. Inc.	USA
	Kronos-Titan G.m.b.H.	Germany
	Nippon Soda	Japan
	Rhone-Poulenc S.A.	France
	Tioxide Chemicals, Ltd.	UK
vanadium alkoxides	Mitsubishi Chemical	Japan
germanium alkoxides	Nippon Soda	Japan
	Mitsubishi Chemical	Japan
zirconium alkoxides	H&ls A.G.	Germany
	Nippon Soda	Japan
	Mitsubishi Chemical	Japan
	Tioxide Chemicals, Ltd.	UK
tantalum ethoxide	Nippon Soda	Japan
	Mitsubishi Chemical	Japan

ALKALI METAL ALKOXIDES

Sodium Methylate. Sodium methoxide [124-41-4] NaOCH₃, mol wt 54.0, is a white, caustic, hygroscopic powder; self-ignition at 70–80°C; purity 97–99% ; density, d₄²⁰ 0.45 g/mL; powder density after loose shaking, 0.45 g/mL; apparent density (packing weight), 0.60 g/mL; medium grain size, 0.07 mm; soluble in methanol (33% in at 20°C), insoluble in hydrocarbons and most common organic solvents.

Manufacture is either by reaction of molten sodium with methyl alcohol or by the reaction of methyl alcohol with sodium amalgam obtained from the electrolysis of brine in a Castner mercury cell (78). Both these methods produce a solution of sodium methylate in methanol and the product is offered in two forms: a 30% solution in methanol, and a solid, which is a dry, free-flowing white powder obtained by evaporating the methanol. The direct production of dry sodium methylate has been carried out by the introduction of methanol vapors to molten sodium in a heavy duty agitating reactor. The solid is supplied in polyethylene bags contained in airtight drums filled in a nitrogen atmosphere.

Typical specifications of the powder are as follows: sodium methylate, 97.5% ; sodium hydroxide, 0.5% ; sodium carbonate, 0.4% ; sodium formate, 0.3% ; and free methanol, 0.5% .

The 30% solution in methanol has the following specifications: sodium methylate content, 29–30% ; density at 20°C, 0.972; viscosity at 30°C, 4.5 Pas (45 P); flash point, 11°C; crystallization temperature, 7°C; miscible in alcohols; immiscible in hydrocarbons.

Sodium Ethylate. Sodium ethoxide [141-52-6], NaOC₂H₅, mol wt 68.1, is a fine yellowish-white, free-flowing, strongly caustic, hygroscopic powder; self-ignition at 30–50°C; purity 94–97% ; density at 20°C, 0.25 g/mL; powder density after loose shaking, 0.20 g/mL; apparent density (packing weight), 0.30 g/mL; medium grain size, 0.01–0.03 mm; easily soluble in ethanol (28%), insoluble in hydrocarbons and most other organic solvents.

Sodium *tert*-Butylate. Sodium *tert*-butoxide [865-48-5], (CH₃)₃CONa, mol wt 96.1, is a pale yellow, free-flowing, caustic, hygroscopic powder; purity 95–99% ; bulk density 0.3–0.4 g/mL; fairly soluble in alcohols, sparingly soluble in ether and hydrocarbons.

Sodium *tert*-Amylate. Sodium *tert*-amylate [14593-46-5], C₂H₅(CH₃)₂CONa, mol wt 110.1, is a white to pale yellow, free-flowing, caustic, hygroscopic powder; purity 95–99% ; bulk density 0.3–0.4 g/mL; fairly soluble in hydrocarbons.

Potassium Methylate. Potassium methoxide [865-33-8], KOCH₃, mol wt 70.13, is a fine, free-flowing, yellowish-white, caustic, hygroscopic powder; purity 96.5–99% ; powder density after loose shaking, 0.75 g/mL; apparent density (packing weight), 1.00 g/mL; medium grain size, 0.05 –0.8 mm; easily soluble in alcohols (33% in methanol at 20°C), insoluble in hydrocarbons.

Potassium Ethylate. Potassium ethoxide [917-58-8], KOC₂H₅, mol wt 84.16, is a fine, yellowish-white, free-flowing, strongly caustic, hygroscopic powder; purity 95–97% ; powder density after loose shaking, 0.65 g/mL; apparent density (packing weight), 0.83 g/mL; medium grain size: 0.15–0.80 mm; easily soluble in alcohols (28% in ethanol or ether at 20°C), insoluble in hydrocarbons; under certain circumstances, self-igniting at room temperature and should therefore be handled under nitrogen.

Potassium *tert*-Butylate. Potassium *tert*-butoxide [865-47-4], (CH₃)₃COK, mol wt 112.2, is a fine, white, caustic, free-flowing, hygroscopic powder; purity 95–99% ; density, d₄²⁰ 0.50 g/mL; powder density after loose shaking, 0.50 g/mL; apparent density (packing weight), 0.70 g/mL; medium grain size, 0.25–0.30 mm; soluble in alcohols (20% in *tert*-butyl alcohol at 20°C) and THF, sparingly soluble in ether and hydrocarbons. In contrast to potassium alkoxides with α-hydrogens, it is more resistant to ignition and oxidation.

ALKALINE EARTH METAL ALKOXIDES

Magnesium Methylate. Magnesium methoxide [109-88-6], Mg(OCH₃)₂, mol wt, 86.3, is an almost white powder; powder density 0.5 g mL; grain spectrum, >500 μm (ca 10° o), 200–500 μm (ca 20° o), <200 μm (ca 70° o); sparingly soluble in methanol, ethanol, and cyclohexane; nearly insoluble in butanol, butyl acetate, and DMF; completely insoluble in ether and hydrocarbons.

Magnesium methylate is sensitive to air and moisture, decomposing to magnesium hydroxide, carbonate, and methanol. It can be stored for one year in polyethylene bags under nitrogen or argon.

Magnesium methylate is used as a drying agent for alcohols and other organic solvents and as an intermediate in various manufacturing processes, eg, for organomagnesium compounds (79), orthocarbonic esters (80), and for oxide coatings.

A significant use is as a catalyst in a multitude of reactions, such as the formation of acrylic and methacrylic acid amides from fatty acid amides (81); of cyclic ketones such as 4-phenylcyclopentane-1,2-dione and 2,5-dihydroxy-*p*-benzoquinone from benzaldehyde diethyl acetal and 2,4-dioxo-5,5-dimethoxy-hexanoic acid methyl ester (82); of dimer aldehydes from propane (83); and for the polymerization of epoxy compounds (84).

Magnesium Ethylate. Magnesium ethoxide [2414-98-4], Mg(OC₂H₅)₂, mol wt 114.4, is an almost white hygroscopic powder; density, d₄²⁰ 0.48 g mL; powder density, 0.48 g mL; grain spectrum, <500 μm, (ca 24° o), 200–500 μm (ca 70° o), <200 μm (ca 6° o); soluble in methanol, ethanol, and DMF, insoluble in ethers and hydrocarbons. It should not be stored longer than one year. It is packaged in polyethylene bags under nitrogen or argon.

Magnesium ethylate is used as a drying agent for organic solvents, as an intermediate for the manufacture of organomagnesium and other organic products, as catalyst in the Tishchenko (85) and other reactions (86–91), in the condensation of esters (92), in alkylaton reactions, and in polymerizations (84,91).

Calcium Methylate Ethylate and Ethylate. Calcium methoxide [2556-53-8] and ethoxide [2914-17-2], Ca(OCH₃)₂ and Ca(OC₂H₅)₂, are white powders soluble in the corresponding alcohol (max concentration 1° o). They are packaged and stored like the magnesium alkoxides.

ALUMINUM ALKOXIDES

Aluminum Isopropylate. In Group 3 aluminum isopropoxide [555-31-7], Al(OCH(CH₃)₂)₃, mol wt 204.25, is a white solid; density, d₄²⁰ 1.0346 g mL; flash point, 26°C; melting point, 118.5°C; boiling point, 140.5°C at 1060 Pa (8 mm Hg); ΔH 82 J mol (19.6 cal mol); easily soluble in alcohols. It is supplied in blocks in 25-kg canisters or as powder in 20-kg tin cans.

The usual method of manufacturing is by direct reaction of aluminum and isopropyl alcohol. In one procedure, aluminum ingots are dissolved in excess isopropyl alcohol, using mercuric chloride or iodine as catalyst; the excess isopropyl alcohol is stripped and the remaining aluminum isopropoxide distilled. In another process (93), the reaction is controlled, requires no catalyst, and gives nearly quantitative yields. The aluminum is contained in a tower above the isopropyl alcohol and the alcohol refluxes through the column, continually washing the product into the stillpot until 100° o concentration is reached. The product is then drawn off and distilled under vacuum. The stillpot is recharged with alcohol and the process is repeated. This process also lends itself to continuous production by continually drawing off product and feeding in alcohol and aluminum. Aluminum isopropoxide can also be produced by the addition of excess isopropyl alcohol to a benzene solution of aluminum chloride, followed by passage of dry ammonia which precipitates ammonium chloride. The ammonium chloride is filtered and the isopropoxide is separated by distillation.

Aluminum *sec*-Butylate Aluminum *sec*-butoxide [2269-22-9], mol wt 246.3, Al(OCH(CH₃)C₂H₅)₃ is miscible with aromatic hydrocarbons; density, d₄²⁰ 0.9671 g mL; flash point, 26°C; bp, 180°C at 53 Pa (0.4 mm Hg); ΔH 90 J mol (21.5 cal mol); degree of association, 2.4.

Aluminum alkoxides are easily soluble in hydrocarbons and in chlorinated hydrocarbons, but sparingly soluble in alcohols. They are sensitive to moisture and dry storage is essential. Aluminum alkoxides are used extensively as intermediates, for example, in the Meerwein-Ponndorf reaction (94).

TRANSITION METAL ALKOXIDES

Titanium Alkoxides. Titanium alkoxides are made from titanium tetrachloride and the corresponding alcohols in the presence of ammonia. Higher titanium alkoxides are manufactured from lower alkoxides by alcoholysis. Titanium isopropoxide and *n*-butoxide are commercially available in barrels. Annual production of titanium alkoxides is estimated at 3000–4000 metric tons at an average price of about \$4 kg.

Titanium alkoxides are used for the hardening and cross-linking of epoxy, silicon, urea, melamine, and terephthalate resins; in the manufacture of noncorrodable, high temperature lacquers; in the sol-gel process; as water repellents and adhesive agents (especially with foils); to improve glass surfaces; as catalyst in olefin polymerization, and for condensation and esterification.

Tetraisopropyl Titanate. Some properties of the ethoxide are noted in Table I. Titanium tetraisopropoxide [546-68-9], Ti[OCH(CH₃)₂]₄, mol wt 284.3, is an almost colorless to light-yellowish fluid, fumes in moist air, soluble in organic solvents; density, d₄²⁰ 0.97 g mL; mp, 15–19°C; bp, 232°C (49°C at 10 Pa or 0.075 mm Hg); flammable, flash point 50–60°C; ΔH 76 J mol (18.2 cal mol); degree of association, 1.4.

Tetrabutyl Titanate. Titanium tetra-*n*-butoxide [5593-70-4], Ti(OC₄H₉)₄, mol wt 340.5, is an almost colorless to light yellow viscous fluid which hydrolyzes in moist air, and is soluble in organic solvents; density, d₄²⁰ 1.00 g mL; solidification point, 50–80° C; bp, ca 300°C (142°C at 10 Pa); flammable, flash point 50–60°C; ΔH 113 J mol (27 cal mol); degree of association, 3.4.

Zirconium Alkoxides. Like the corresponding titanium compounds, the zirconium alkoxides are manufactured from solid zirconium tetrachloride and the respective alcohol in the presence of ammonia. Higher alkoxides are manufactured by alcoholysis. Zirconium *n*-propoxide and *n*-butoxide are commercially available in barrels at about \$14 kg.

Zirconium alkoxides are used for cross-linking and hardening of isocyanate, epoxy, silicon, urea, melamine, and terephthalate resins; in the sol-gel process; as catalysts in condensation; and as water repellents. Zirconium alkoxides hydrolyze in moist air, but more slowly than titanium alkoxides.

Zirconium Tetra-n-propylate. Zirconium tetra-*n*-propoxide [23519-77-9], Zr(OC₃H₇)₄ mol wt 327.6, is a colorless solid, melting point, 214°C (95). The commercial product contains about 28° o ZrO₂ and propanol; it is a yellow-brown liquid, density, d₄²⁰ 1.05 g mL; solidification point below 70° C; flammable, flash point below 21°C, soluble in hydrocarbons.

Zirconium Tetra-n-butylate. Zirconium tetra-*n*-butoxide [1071-76-7] Zr(OC₄H₉)₄ mol wt 383.7, is a colorless solid, melting point, 134°C (95). The commercial product contains about 28° o ZrO₂ and butanol; it is a yellow-brown liquid, density (apparent), d₄²⁰ 1.07 g mL; solidification point below 70° C; bp, 260°C at 10 Pa (0.075 mm Hg); flammable, flash point 21°C; soluble in hydrocarbons.

Vanadium Alkoxides. Except for the solid methoxide, the lower vanadium alkoxides are slightly colored, yellow, or yellow-brown liquids. They are easily hydrolyzed and decompose on heating; above 100°C they darken. They are made from V₂O₅ or VOCl₃.

Vanadium alkoxides are used mostly in olefin polymerization as catalysts; also as hardeners and for coatings.

Of importance, besides the ethoxide and the isopropoxide, is vanadium *n*-butoxide [1801-76-9] (vanadyl butylate), mol wt 286.3, a yellow liquid; bp, 135°C; density, d₄²⁰ 1.03 g mL. For further information about vanadium alkoxides, see references 22, 23, 96, 97.

ANTIMONY TRIALKOXIDES

With the exception of the solid methoxide [19727-40-3], the lower antimony trialkoxides are colorless or slightly colored distillable liquids, easily hydrolyzed. Thermally these alkoxides are rather stable. The lower antimony trialkoxides are manufactured from antimony trichloride, the higher from antimony trioxide, both on a small scale. They are used in polyester manufacture, in fireproofing, as catalysts, and for coatings. For further information about antimony trialkoxides, see references 21, 65, 98.

Handling, Shipment, and Toxicology

Metal alkoxides are strongly caustic and are decomposed by the humidity of the air or moisture of the skin, requiring the use of protective glasses and gloves.

The heat of hydrolysis, $MOR + HOH \rightarrow MOH + ROH$ (exothermic), is capable of igniting alkali alkoxides, especially potassium alkoxides, on exposure to air. Such fires must be extinguished with sand or foam but not with water.

Alkoxides should be stored under cool, dry conditions. The solids are packed in polyethylene bags under nitrogen or argon that are shipped in drums with foam rubber gaskets. For the liquid alkoxides steel drums are used, usually with a polyethylene liner.

The health hazard presented by metal alkoxides reflects the toxicity of the metals they contain and the metallic hydroxides and alcohols they form on hydrolysis.

Analytical Methods

The ease of hydrolysis of metal alkoxides makes metal analysis a comparatively simple task. In many cases, the metal may be estimated by hydrolysis of a sample in a crucible, and ignition to the metal oxide. Alternatively, the metal ion may be brought into solution by hydrolysis of a sample with dilute acid, followed by a standard analytical procedure for a solution of that particular metal. If the alcohol liberated during the hydrolysis is likely to cause interference, it may be distilled from the solution by boiling.

The estimation of alkoxy groups is not such a simple task. One method (26,68) involves hydrolysis and oxidation of the liberated alcohol with excess standard potassium dichromate solution. The excess may then be estimated iodometrically. This method is suitable only for methoxides, ethoxides, and isopropoxides; quantitative conversion to carbon dioxide, acetic acid, and acetone, respectively, takes place. An alternative method for ethoxides is oxidation followed by distillation, and titration of the liberated acetic acid.

For the higher alkoxy groups, standard carbon and hydrogen analysis may be used, although careful sample preparation is required because of the ease of hydrolysis. Quantitative vapor-phase chromatography of alcohol liberated during hydrolysis may also be used, but care must be taken in this case to ensure that hydrolysis is complete before the estimation is carried out.

Applications

Metal alkoxides are used for a great variety of purposes (99). They are useful for putting a metal into an organic solution, for instance in a homogeneously catalyzed reaction. When a metal must be fixed onto an organic or inorganic surface, it may be done by reaction of a suitable alkoxide with active groups of the surface.

They compete with other inorganic metal compounds, such as metal carboxylates, and have advantages because of their catalytic properties, ease of hydrolysis, solubility in organic solvents, and distillability. They are mainly used as catalysts (in Ziegler-Natta polymerization, transesterifications, and condensations), with partial or complete hydrolysis, alcoholysis, transesterification in coatings for plastics, textiles, glass, and metals, and in additives for adhesives and paints, for sol-gel applications (51–54), for synthesis of minerals capable of safely enclosing radioactive nuclear waste (54,100–103) and for the cross-linking or hardening of natural and synthetic materials. Alkali metal alkoxides find their principal use in organic synthesis where they act as strong bases.

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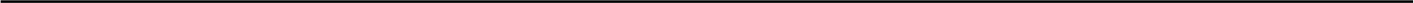
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ALKYD RESINS

Alkyd resins have been the workhorse for the coatings industry since the 1940s. The term "alkyd" was coined to define the reaction product of polyhydric *al*cohols and polybasic *acids*, in other words, polyesters. However, its definition has been narrowed to include only those polyesters containing monobasic acids, usually long-chain fatty acids. Thus thermoplastic polyesters typified by poly(ethylene terephthalate) (PET) used in synthetic fibers, films, and plastics, and unsaturated polyesters typified by the condensation product of glycols and unsaturated dibasic acids, that are widely used in conjunction with vinylic monomers in making sheet molding compounds (SMC) or other thermosetting molded plastics, are not considered part of the alkyd family. Detailed discussions of those subjects can be found elsewhere in this Encyclopedia (see FIBERS, POLYESTER; POLYESTERS, THERMOPLASTIC; POLYESTERS, UNSATURATED).

The first appearance of the term "alkyd resin" in the subject index of *Chemical Abstracts* was in 1929, under Resins. It was not until 1936 that Alkyd Resins was listed in its alphabetical place, but still appeared as "See Resinous Products." The proliferation of literature on alkyd resins peaked from the 1940s through the 1960s. Research activities on alkyds in the United States, as indicated by the number of publications, has apparently tapered off since the 1970s. Readers interested in alkyd history can find more detailed historical reviews elsewhere (1–4).

In spite of challenges from many new coating resins developed over the years, alkyd resins as a family have maintained a prominent position for two principal reasons. First, alkyds are extremely versatile. An alkyd technologist can choose from a large variety of reaction ingredients at widely different ratios to tailor the structure and properties of the resin, or to obtain similar resin properties from different ingredients as their availability or cost may sometimes so dictate. For almost any given coating application, from baking enamels for appliances to flat house paints to clear wood finishes, an alkyd resin can be designed to meet the property requirements. The second reason for the continued importance of alkyd resins is that they can be made at relatively low cost. Most of the raw materials are fairly low cost commodity items, and major capital investment and high processing costs are not needed to produce the resins.

Fundamental Reactions and Resin Structure

The main reactions involved in alkyd resin synthesis are polycondensation by esterification and ester interchange. Figure 1 uses the following symbols to

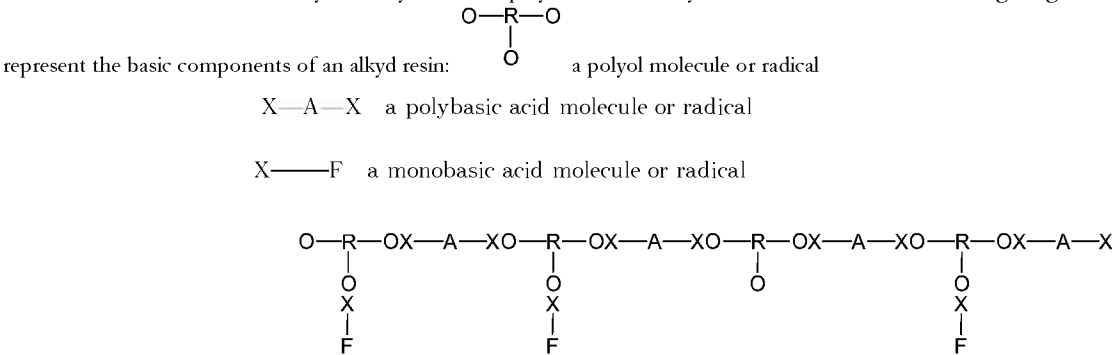


Fig. 1. Schematic representation of an alkyd resin molecule.

As Figure 1 implies, there is usually some residual acidity as well as free hydroxyl groups left in the resin molecules. Structure-property relationships and the principles commonly followed to design the resin structure are discussed later.

CLASSIFICATION OF ALKYD RESINS

Alkyd resins are usually referred to by a brief description based on certain classification schemes. From the classification the general properties of the resin become immediately apparent. Classification is based on the nature of the fatty acid and oil length.

Drying vs Nondrying, and the Specific Source of Fatty Acids. Alkyd resins can be broadly classified into drying and nondrying types depending on the ability of their films to dry by air oxidation. This drying ability is derived from the polyunsaturated fatty acids in the resin composition. If drying oils, such as linseed oil (which has substantial unsaturation), are the sources of the fatty acids for the alkyd, the resin belongs to the drying type and is usually used as the film former of coatings or inks (see DRYING AGENTS). On the other hand, if the fatty acids come from nondrying oils, such as coconut oil (which has very little unsaturation), the resin is a nondrying alkyd. They are used either as plasticizers for other film-formers, such as in nitrocellulose lacquers, or are cross-linked through their hydroxyl functional groups to become part of the film-former. More frequently, an alkyd resin is classified by the source of the fatty acids, eg, a linseed alkyd, a tung oil modified soya alkyd, or a coconut alkyd.

Classification by Oil Length or Fatty Acid Content. The amount of fatty acid modification in the polyester structure of an alkyd resin prescribes such properties as solubility, compatibility, and film hardness of the resin. Therefore, this is the most frequently encountered way of classifying alkyd resins. This practice was probably inherited from the oleoresinous varnish scheme but with a different manner of expression. The oil length of a varnish is defined as the number of gallons of oil per one hundred pounds of resin in the varnish. For an alkyd resin, the oil length is defined as the weight percent of oil or triglyceride equivalent, or alternatively, as the weight percent of fatty acids in the finished resin. Using the resin represented in Figure 1 as an example, the structure indicates that the molar ratio of the three ingredients is 4:4:3. Assuming that the polyol is glycerol, the polybasic acid is phthalic anhydride, and the fatty acids come from soybean oil with an average mol wt of 280, the formula weight of the resin is then 1674, the triglyceride equivalent of the fatty acids, 878, and the oil length, 52.4%. Alternatively, this resin is described as one having 50.2% fatty acids (840 parts fatty acid in 1674 parts of finished resin). Since the overwhelming majority of alkyd resins is based on phthalic anhydride, it is also customary to describe an alkyd in terms of its phthalic anhydride content in percent based on the finished resin.

Alkyd resins are classified into four classes by oil length:

Resin class	Oil, %	Fatty acids, %	Phthalic anhydride, %
very long	over 70	over 68	below 20
long	56–70	53–68	20–30
medium	46–55	43–52	30–35
short	below 45	below 42	over 35

These demarcations are arbitrary and the boundaries are usually not clear cut.

More frequently, alkyd resins are described by a combined classification in terms of their oil length, the type of fatty acids, and any unusual ingredients. Such descriptions as an isophthalic, very long tall oil alkyd; a medium oil dehydrated castor-PE (pentaerythritol, not polyethylene) alkyd; or a short oil lauric-benzoic alkyd, immediately project the general properties of the resin.

OIL LENGTH-RESIN PROPERTY RELATIONSHIP

The oil length of an alkyd resin has profound effects on the properties of the resin.

Solubility. At long oil lengths, the aliphatic hydrocarbon chains of the fatty acids constitute the major portion of the mass of the resin molecules; therefore, the resin is soluble in nonpolar aliphatic solvents. Conversely, as the oil length decreases and the phthalic content increases, the aromaticity of the resin molecules increases, and the aromaticity and or the polarity of the solvent must be increased in order to dissolve the resin effectively.

Drying Characteristics. Alkyd resin molecules have a comblike structure, with a thermoplastic polyester backbone and dangling fatty acid side chains. Each fraction contributes to the drying, or film-forming, characteristics of the resin. The backbone fraction dries by solvent release, similar to a lacquer material, whereas the side-chain fraction dries in a manner similar to the oil from which the fatty acid came. Therefore, short oil alkyds develop a lacquer-type dryness relatively quickly due to faster solvent release, which is often further facilitated by the fact that the solvents used have high volatility. However, the through-dry derived from side-chain cross-linking is usually slower because the fatty acid side chains are fewer in number and more scattered in space, thus impeding cross linking with each other through the action of oxygen, and the dry surface impedes the transportation of air oxygen down into the film. On the other hand, long oil alkyds are relatively slow in reaching the "set-to-touch" stage of surface drying, but the greater abundance of fatty acid side chains and the relative openness of the film surface facilitate the oxidative cross-linking reaction in the film for reaching through-dry.

Other trends in properties with changes in oil length are summarized in Table 1.

Table 1. Property Changes With Oil Length of Alkyd Resins^a

Oil length	Long	Medium	Short
requirement of aromatic polar solvents			
compatibility with other film-formers			
viscosity			
ease of brushing			
air dry time, set-to-touch			
through-dry			
film hardness			
gloss			
gloss retention			
color retention			
exterior durability			

^a Primarily drying-type alkyds.

Theoretically, alkyd resins can be designed at almost any oil length. However, for any given set of starting ingredients, a point is reached at which the maximum extent of fatty acid modification of the polyester molecules has been achieved, and any additional amounts of fatty acid or oil remain as separate entities blended with the polyester molecules. Referring again to the resin structure in Figure 1, if the molar ratio between glycerol and phthalic anhydride is fixed at 1:1 and assuming that the phthalic carboxyl groups react completely, the maximum amount of soya acid that can be attached to the resin is one mole per mole of glycerol, which gives an oil length of 60.5° o, or 57.9° o of soya fatty acids. If the molar ratio between glycerol and phthalic anhydride is variable, the fatty acid content can be increased much further by adding more glycerol, which results in a shortening of the average chain length of the resin molecules. A maximum (soya) oil length of 86° o or fatty acid content of 82.2° o is reached when phthalic anhydride:glycerol:fatty acid becomes 1:2:4 on a molar basis. (The "resin" molecules are, thus, statistically monomer). Additional oil or fatty acid cannot be incorporated into the resin molecules, and is retained in the resin as a blend. Obviously, polyols with higher functionality can carry more fatty acids, thus reaching higher oil length. Oil length expresses the weight percent, not mole percent, of the oil or fatty acids in the resin. Thus an equimolar substitution of a longer chain fatty acid with a shorter one, eg, substituting stearic acid with lauric acid, results in a reduction in oil length.

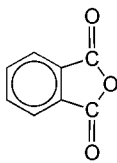
Alkyd Ingredients For each of the three principal components of alkyd resins, the polybasic acids, the polyols, and the monobasic acids, there is a large variety to be chosen from. The selection of each of these ingredients affects the properties of the resin and may affect the choice of manufacturing processes. Thus, to both the resin manufacturers and the users, the selection of the proper ingredients is a significant decision.

Polybasic Acids and Anhydrides. The principal polybasic acids used in alkyd preparation are listed in Table 2.

Table 2. Polybasic Acids Used in Alkyd Resin Preparation

Common name	CAS Registry Number	Systematic name	Mol wt	Eq wt
phthalic anhydride	[85-44-9]	1,2-benzene dicarboxylic anhydride	148	74
isophthalic acid	[121-91-5]	1,3-benzene dicarboxylic acid	166	83
maleic anhydride	[108-31-6]	cis-butenedioic acid anhydride	98	49
fumaric acid	[110-17-8]	trans-butenedioic acid	116	58
adipic acid	[124-04-9]	hexanedioic acid	146	73
azelaic acid	[123-99-9]	nonanedioic acid	160	80
sebacic acid	[111-20-6]	decanedioic acid	174	87
chlorendic anhydride	[115-27-5]	1,4,5,6,7,7-hexachlorobicyclo[2.2.1]-5-heptene-2,3-dicarboxylic anhydride	371	185.5
trimellitic anhydride	[552-30-7]	1,2,4-benzenetricarboxylic acid anhydride	192	64

Phthalic anhydride is the most important type of dibasic acid derivative in alkyd preparation because of its low cost and the excellent overall properties it imparts to the resin. The anhydride structure allows a fast esterification to form half-esters at relatively low reaction temperatures without liberating water, thereby avoiding the danger of excessive foaming in the reactor. However, since the two carboxyl groups of phthalic anhydride are in the ortho position to each other on the benzene ring, cyclic structures may and do occur in the resin molecules.



Consequently, the development of chain length of the polymer is restricted and the average molecular weight tends to be low. Phthalic anhydride has a tendency to sublime. Its heat of sublimation is 598 J g (143 cal g), and the heat of vaporization is 365 J g (87.2 cal g). Therefore, care must be taken to prevent its loss (see later discussions on Production Processes).

Isophthalic acid is the meta isomer of phthalic acid. Since the two carboxyl groups are separated, the chances of forming a cyclic structure in the resin molecules are diminished. Therefore, isophthalic alkyds usually attain higher molecular weight and show much higher viscosity than their phthalic counterparts at the same oil length. This is the principal motivation for resin manufacturers to use isophthalic acid for the preparation of their very long oil alkyds. Another advantage of isophthalic acid is that the resultant alkyd resins show much higher thermal stability than the phthalic type (5). In spite of these advantages, isophthalic acid has not gained the same popularity as phthalic anhydride in alkyds, because the resin making process with it is much more complicated and difficult. Isophthalic acid's melting point (350°C) is much higher than that of phthalic anhydride (131°C), and it has very low solubility in the initial alkyd reactants, which causes the reactants to stay as a two-phase solid-liquid system that does not become clear until the reaction is nearly complete (6,7). Additional care and equipment are needed for the higher processing temperature required for isophthalic acid. Unlike phthalic anhydride, the diacid does not form half-esters at relatively low reaction temperature, and twice as much water from esterification is formed and must be removed compared to the anhydride.

Terephthalic acid [100-21-0], the para isomer, may be, but is rarely, used in making alkyds. The resultant resins have even better thermal stability than isophthalic alkyds (5). However, it has all the disadvantages of isophthalic acid and is more expensive.

Maleic anhydride is sometimes used for partial substitution of phthalic anhydride in making alkyds. It imparts vinylic unsaturation to the backbone chain of the resin molecules and thus allows the resin to be grafted with styrene, acrylic esters, or other vinyl monomers. The presence of a small amount of maleic anhydride, up to 10 mol % of the total dibasic acids in the resin formulation, accelerates the viscosity increase during the resin manufacturing process. The resins usually dry more rapidly and give harder films with improved color, adhesion, water resistance, alkali resistance, and exterior durability. However, the resin cooking process must be monitored and controlled with greater care, particularly when it is near the desired endpoint, to prevent gelation. Fumaric acid, the trans isomer of maleic acid, may be used in an equivalent manner.

Maleic acid and fumaric acid can also be, and are often, incorporated in alkyd resins in the form of the Diels-Alder adduct of rosin. The adducts are tribasic acids which provide pendent carboxyl groups in the resin molecules, which can be saponified to give ionic, and, in turn, water-soluble characteristics to the resin. However, the resultant alkyds often have poorer color retention, toughness, gloss retention, and exterior durability.

Aliphatic dibasic acids, such as succinic acid, adipic acid, azelaic acid, and sebacic acids have also been used to make alkyd resins. Their linear chain structure lends higher flexibility and lower viscosity to the resin as compared to the rigid aromatic rings of phthalic acids.

Chlorendic anhydride is the common name of the Diels-Alder adduct of maleic anhydride and hexachlorocyclopentadiene, 3,4,5,6,7,7-hexachloroendomethylene-1,2,3,6-tetrahydrophthalic anhydride (HET). The resultant resins from HET contribute to the flame retardancy of the alkyd coatings. HET gives a greater reaction rate than phthalic anhydride, to the extent that at 204–210°C the reaction rate approximates that of phthalic anhydride at a temperature of 238°C (8). However, the resins tend to develop darker color, particularly at high processing temperature. Tetrachlorophthalic anhydride [117-08-8], made by conventional chlorination of phthalic anhydride, would also impart flame retardancy to its alkyds. However, it is appreciably less soluble in the usual processing solvents than is phthalic anhydride, and is reported to be of appreciably lower chemical reactivity (8).

Trimellitic anhydride (TMA). 1,2,4-Benzenetricarboxylic acid anhydride, has gained greater prominence in recent years due to the greater interest in water-soluble alkyds. Partial substitution of phthalic anhydride with TMA gives a measurable quantity of pendent carboxyl groups for water solubilization with ammonia or other suitable bases. The anhydride hydrolyzes to the acid form simply by allowing it to stand in open containers. Premature cross-linking of alkyd resins formulated with a high content of TMA can occur at high acid numbers if large amounts of trimellitic acid are present (9).

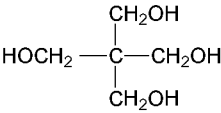
Polyhydric Alcohols. The principal types of polyol used in alkyd synthesis are shown in Table 3.

Table 3. Polyols for Alkyd Synthesis

Type	CAS Registry Number	Mol wt	Eq wt
pentaerythritol	[115-77-5]	136	34
glycerol	[56-81-5]	92	31 ^a
trimethylolpropane	[77-99-6]	134	44.7
trimethylolethane	[77-85-0]	120	40
ethylene glycol	[107-21-1]	62	31
neopentyl glycol	[126-30-7]	104	52

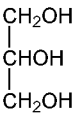
^a Because glycerol is usually supplied at 99% purity (1% moisture), its eq wt is commonly assumed to be 31 in recipe calculations.

Pentaerythritol (PE) is one of the most important polyols used in alkyd resins. Its molecular structure is the basis for its many interesting attributes.



The four equal and highly reactive primary hydroxyl groups make it very versatile for designing resin structures, and the neopentyl core structure lends stability against heat, light, and moisture. As a result, alkyds based on PE usually are superior to their counterparts based on glycerol in viscosity, drying properties, film hardness, gloss retention, color and color stability, humidity resistance, thermal stability, and exterior durability (10). On the other hand, its high functionality demands that the resin composition be more carefully designed and the synthesizing process be more carefully monitored and controlled to reduce or eliminate the tendency of gelation. Dipentaerythritol [126-58-9] and tripentaerythritol [78-24-0] are the linear dimer and trimer of PE. They are hexa- and octa- functional polyols, respectively. Technical grades of PE usually contain small or trace quantities of di- and tri-PE that were not completely removed in the manufacturing process. Their high tendency toward cross-linking due to their high functionality makes them impractical for consideration as the sole or principal polyol of an alkyd resin except for achieving a very long oil length along with reasonably high molecular weight in the resin.

Glycerol is undoubtedly the most important triol in alkyd technology.



Natural fats and oils are triglycerides. Therefore, whenever oils are used directly as the source of fatty acids in an alkyd resin, glycerol is automatically a part of the polyols of the resin. Besides the difference in numbers of hydroxyls in glycerol and PE, one of the hydroxyl groups in glycerol is secondary, which has lower reactivity compared to primary hydroxyl groups. Furthermore, at high temperatures and under acidic conditions, glycerol may undergo dehydration to give water and acrolein (CH₂=CHCHO), whereas such a reaction is not possible with PE. These characteristics often give the appearance that glycerol has a functionality of less than three. Consequently, larger excesses of glycerol are often required in the resin formulation, resulting in poorer resin properties as a coating material. Glycerol alkyds are more prone to thermal decomposition to give color bodies, resulting in darkening of the resin.

Trimethylolethane and *trimethylolpropane* are synthetic triols. Similar to PE, they have the neopentyl structure, and equivalent primary hydroxyl functional groups. Therefore, they also yield alkyds with better resistance to heat, light, moisture, and alkali than glycerol. Relative to PE, they have one less hydroxyl group, and the equivalent weights of these polyols are higher than that of PE. Relative to each other, trimethylolethane has been reported to give alkyds that are faster drying and have higher film hardness than trimethylolpropane (11), whereas trimethylolpropane was claimed to give alkyds with better water and alkali resistance, color and color retention, and impact resistance than trimethylolethane (12).

Diols such as ethylene glycol, propylene glycol [57-55-6], and neopentyl glycol are sometimes used as part of the polyols in alkyd formulations primarily for the purpose of regulating the functionality of the reaction system. Their relatively low boiling points, ~200° C, require that special precautionary measures be taken during the resin manufacturing process.

Polyols. Analogous to the use of linear α,ω-dibasic acids, such as adipic and sebacic, polyols with long, flexible chains between hydroxyl groups, such as 1,4-butanediol [110-63-4], 1,6-hexanediol [629-11-8], and diethylene glycol [111-46-6], may also be used to impart greater flexibility in the resin.

Under high temperatures, such as those used for alkyd resin synthesis, and in the presence of high acidity, etherification between the hydroxyl groups of two polyol molecules may produce a new polyol with a functionality of $n + n' - 2$, where n and n' are the numbers of hydroxyl groups of the two original molecules. The introduction of such high functionality polyols, plus the net reduction of total available hydroxyl groups can lead to an increased danger of gelation during the polycondensation process.

Monobasic Acids. The overwhelming majority of monobasic acids used in alkyd resins are long-chain fatty acids of natural occurrence. They may be used in the form of oil or free fatty acids (see FATS AND FATTY OILS). Free fatty acids are usually available and classified by their origin, viz, soya fatty acids, linseed fatty acids, coconut fatty acids, etc. Fats and oils commonly used in alkyd resins are given in Table 4.

Table 4. Fatty Acid Compositions, Wt %, of Fats and Oils Commonly Used in Alkyd Resins

Fat or oil	Iodine value	Saponification value	Saturated acids				Monoethenoic acids		Diethenoic acid	Triethenoic acid	Other acids
			C12	C14	C16	C18	C16	C18	C18	C18	
			Lauric acid [143-07-7]	Myristic acid [544-63-8]	Palmitic acid [57-10-3]	Stearic acid [57-11-4]	Palmitoleic acid	Oleic acid	Linoleic acid	Linoleic acid	
castor oil	85.8	195		2.4				7.4	3.1		Ricinoleic acid [141-22-0], 87.0; dihydroxystearic acid, 0.6
coconut oil	8.7	257	48.0	17.5	9.0	2.1		5.7	2.6		Caprylic acid [124-07-2], 7.9; Capric acid [344-48-5], 7
cottonseed oil	105.0	196		1.4	23.4	1.1	2.0	22.9	47.8		Tetradecenoic acid, 0.1
linseed oil	179.8	191			6.3	2.5		19.0	24.1	47.4	Lignoceric acid [557-59-5], 0.2
oiticica oil ^a		192		11.3				6.2			Licanic acid [17699-20-6], 82.5
peanut oil	93.3	190		0.5	7.8	3.1	1.7	54.3	26.0		Arachidic acid [506-30-9], 2.4; Behenic acid [112-85-6], 3.1; Lignoceric acid, 1.1
rapeseed oil	102.3	175			1.9	3.5	1.5	12.3	15.8	8.7	Behenic acid, 0.7; Lignoceric acid, 0.8; Eicosenoic acid, 4.8; Erucic acid [112-86-7], 47.8; Docosendienoic acid, 1.5
safflower oil	136.2	191	0.4	1.1	2.9	1.1		32.8	61.1	0.1(?)	
soyabean oil	132.6	193		0.4	10.6	2.4	1.0	23.5	51.2	8.5	sat(d) C20–24 acids, 2.4
sunflowerseed oil	130.8	188			3.6	2.9		34.0	57.5		Lignoceric acid, 0.4
tung oil	^a	192		5.0				5.0	3.0		Eleostearic acid [16684-29-0], 87

^a Owing to incomplete halogen absorption, iodine values for conjugated acid oils by the usual methods (Wijs, Hanus, etc) are both low and variable. The true value of fresh tung oil, as determined by a special method (13), is 248–252; that of oiticica oil is 205–220.

The drying property of fats and oils is related to their degree of unsaturation, hence, iodine values. A generally accepted rough classification considers those with iodine values (Wijs method) below 90 to be nondrying, between 90 and 130 to be semidrying, and above 130 to be drying. Thus monoethenoic acids, such as oleic acid [112-80-1] and palmitoleic acid [373-49-9], contribute very little to air-drying ability; polyunsaturation is needed. The drying ability is further enhanced when the unsaturated groups are conjugated to each other. Thus dehydrated castor oil has outstanding drying capability; tung oil and oiticica oil, with their conjugated trienes, dry much faster than other drying oils. In fact, tung and oiticica oil dry so fast that if not properly moderated, the surface layer dries long before the underlayer, and results in a wrinkled surface due to the stresses created in the dried surface layer. Therefore, in alkyd resins, tung oil and oiticica oil are primarily used to furnish only a minor portion of the fatty acids to improve drying properties. Even so, great care must be exercised during the manufacturing process to avoid gelation, which is caused by the dimerization of the fatty acid chains through a Diels-Alder addition between the conjugated diene structure on one molecule and a double bond on another molecule. Nonconjugated diene groups, such as those in linoleic acid [60-33-3] and linolenic acid [463-40-1], may undergo isomerization to become conjugated. Furthermore, ene reactions can occur between two unsaturated fatty acid chains which lead to gelation.

Linolenic acid is responsible for the high yellowing tendency of alkyds based on linseed oil fatty acids (14). Therefore, alkyds intended for making white or light color enamels should avoid high linolenic content fatty acids by choosing soya, safflower, or dehydrated castor oil (DCO). Alkyds made with nondrying oils or their fatty acids have excellent color and gloss stability. They are frequently the choice for white industrial baking enamels and lacquers.

Since the mid 1950s, tall oil fatty acids (TOFA) have become available in good qualities and large quantities (see CARBOXYLIC ACIDS, FATTY ACIDS FROM TALL OIL). Refined grades of TOFA have degrees of unsaturation rivaling that of soya acids. Since it is a year-round by-product from the paper industry, its

supply and price are more stable than agricultural products like soya fatty acids, and it is used extensively in medium to long oil alkyds, virtually as equivalent to soya fatty acids. Although the minor quantities of rosin acids in TOFA may impart some yellowing tendency, it is compensated by its lack of linolenic acid and can give as good or even better color retention than soya fatty acids. Typical properties of refined grades of commercial TOFA are given in Table 5.

Table 5. Typical Properties of Refined Tall Oil Fatty Acids

Grade designation	Pamak 1	Pamak 2	Pamak 4A	Pamak 4	Pamolyn 200 ^a	Pamolyn 300 ^b
acid number	193	192	191	188	195	196
iodine number	125	128	130	131	162	156
total fatty acids, %	96.8	95.9	94.1	91.5	97	97
sat(d) acids, % of ffa ^c	2.0			4.0	<1	<1
oleic	51.0			51.0	22.0	21.0
linoleic, nonconjugated	41.0			39.0	68.0	39.0
linoleic, conjugated	6.0			6.0	10.0	40.0
rosin acids, %	1.4	1.8	3.5	4.0	1.5	1.5
unsaponifiables, %	1.8	2.3	2.4	4.5	1.5	1.5
color, Gardner	3	3	4	6	3 +	3
titer, °C	5	5	5	6	28	28

^a Enriched polyunsaturated fatty acids from highly refined TOFA.
^b Same as above, with further treatment to isomerize the nonconjugated linoleic acid.
^c Free fatty acids.

A number of monobasic acids that are not derived from fats and oils have been used in alkyd resins. However, except in the rare cases of making the so-called oil-free alkyds for special purposes, they are used in conjunction with fatty acids to modify resin properties. Rosin acids, primarily abietic acid [514-10-3], may be used in neat form or be brought in as a part of TOFA. Presumably, the fused ring structure of rosin contributes to the film hardness, initial gloss, and water resistance of the alkyd. However, color and color retention, and exterior durability are adversely affected if the rosin content goes much above 5–6%. The drying rate of alkyds usually appears to be improved with rosin modification. However, since rosin does not participate in the oxidative drying mechanism that applies to polyunsaturated fatty acids, the true drying rate of the alkyd resin is actually reduced due to a reduction of the fatty acid unsaturation. Synthetic saturated carboxylic acids, such as pelargonic acid [112-05-0], 2-ethylhexanoic acid [149-57-5], isooctanoic acid, and aromatic monobasic acids such as benzoic acid [65-85-0], and *p*-alkylbenzoic acids, can give even better color retention, gloss retention, and exterior durability but less flexibility than those based on castor or coconut fatty acids. The aromatic acids, similar to rosin, also give higher film hardness and faster apparent drying rate.

The Concept of Functionality and Gelation

The concept of functionality and its relationship to polymer formation was first advanced by Carothers (15). Flory (16) greatly expanded the theoretical consideration and mathematical treatment of polycondensation systems. Thus if a dibasic acid and a diol react to form a polyester, assuming there is no possibility of other side reactions to complicate the issue, only linear polymer molecules are formed. When the reactants are present in stoichiometric amounts, the average degree of polymerization, $\bar{x}_n$, follows the equation:

$$\bar{x}_n = \frac{1}{1 - p}$$

1

where *p* is the fractional extent of reaction. Thus when the reaction is driven to completion, theoretically, the molecular weight approaches infinity and the whole mass forms one giant polymer molecule. Although the material should theoretically still be soluble and fusible, the molecular weight would be so high that it would not be processible by any of the existing methods. For all practical purposes it is a gel; this is the sole example of difunctional monomers being polymerized to gelation.

The functionality of the system, *f*, is the sum of all of the functional groups, ie, equivalents, divided by the total number of moles of the reactants present in the system. Thus, in the above equimolar reaction system,

$$f = \frac{(1 \times 2 + 1 \times 2)}{(1 + 1)} = 2$$

When there are reactants with three or more functionalities participating in the polymerization, branching and the formation of intermolecular linkages, ie, cross-linking of the polymer chains, become definite possibilities. If extensive cross-linking occurs in a polymer system to form network structures, the mobility of the polymer chains is greatly restricted. Then the system loses its fluidity and transforms from a moderately viscous liquid to a gelled material with infinite viscosity. The experimental results of several such reaction systems are collected in Table 6.

Table 6. Gel Points of Polyesterification Reaction Systems with Stoichiometric Reactants^a

Polybasic acid, (COOH) ^b	Polyol, (OH) ^b	Functionality, <i>f</i>	Esterification at gel point, %
adipic ^c + tricarballic acid ^d	diethylene glycol	2.103	91.1
dibasic	glycerol	2.400	76.5
adipic	pentaerythritol	2.667	57.8

^a Ref. 16.
^b Molar proportion = 1.0 unless otherwise noted.
^c [COOH] = 0.707.
^d [COOH] = 0.293.

When the reactants are present in stoichiometric proportions, gelation occurs before the completion of esterification, and the extent of reaction *p*, reached at the gel point, depends on the functionality of the system. The mathematical treatment of Carothers (17) showed that at the gel point, the extent of reaction, $p = 2 / f$. Thus, in order to avoid premature gelation, the polymerization system should have an average functionality of no more than two. This can be accomplished by adding low functionality reactants, and or by adding an excess amount of one of the reactants, usually the one of higher functionality. This has the net effect of reducing the functionality of the reactant. For example, if a 20% excess of glycerol over the stoichiometric amount required to esterify all of the carboxyl groups is added, the glycerol has an effective functionality of 3 / 1.2, or 2.5. Frequently, both of these measures, ie,

addition of monofunctional and excess highly functional components, are taken to safeguard against premature gelation. For alkyd resins, the extent of the reaction at the gel point (18) is

$$p_c = \frac{2}{f} \frac{1}{1 - 2m_0/e_0}$$

where e_0 is the total effective equivalent of all of the reactants present at the beginning of the reaction, ie, the excess reactants are discounted in the manner discussed above, m_0 is the total number of moles of all reactants at the beginning, and f , therefore, is the effective average functionality of the formulation.

Microgel Formation and Molecular Weight Distribution

The behavior of alkyd resin reactions often deviates from that predicted by the theory of Flory (19). To explain this, a mechanism of microgel formation by some of the alkyd molecules at a relatively early stage of the reaction was proposed (19). The microgel particles are dispersed and stabilized by smaller molecules in the remaining reaction mixture. As polyesterification proceeds, more microgel particles are formed, until finally a point is reached where they can no longer be kept separated. The microgel particles then coalesce or flocculate, phase inversion occurs, and the entire reaction mass gels. The drying capability of an alkyd resin comes primarily from the microgel fraction (19). For example, when the highest molecular weight fraction representing about 20% of the total was removed through fractionation, a residual linoleic alkyd lost all ability to air dry to a hard film.

In a further elaboration (20–21) of the formation of micelles as precursors of microgels was proposed. Thus, when some of the molecules have grown to reach certain fatty acid–polyester ratios, surface activity develops to form micelles. Polyesterification reactivity at the surface of the micelles is preferentially greater, which leads to the eventual formation of microgels. Electron microscopy evidence indicated that the size of microgels increases with reaction time, and particle diameters as large as 2 μm have been reported. Functional groups such as OH groups in the microgel particles are believed to be buried in the structure and not available for reactions. Unlike in polyesterification reactions without fatty acids, where at all stages of the reaction, up until the physical gelation of the reaction mixture, the hydroxyl values correspond with the calculated values. Furthermore, the oil-free systems show no sign of microgel formation under the electron microscope, and the reaction mixture undergoes a sudden change from a soluble polymer to a gelled mass. The reaction temperature for alkyd preparation in the systems observed (20,21) was kept at no more than 200°C, well short of what would normally be required for the bodying of unsaturated oils in the absence of an oxidizing reagent. This indicates that polymerization between unsaturated fatty acids of the resin molecules is not necessary for the formation of microgels.

More recently, the formation of microgels was further confirmed by characterization of fractions of alkyd resins from preparative gpc columns (22–25). The presence of microgel can be detected even in low mol wt fractions. Colloidal gel particles up to 10 μm in diameter were observed in the high mol wt (>10⁶) fractions, with or without unsaturated fatty acids in the alkyd formulation. However, the unsaturated fatty acids made a significant contribution to the formation of the colloidal particles. Higher reaction temperature led to higher mol wt and broader mol wt distribution. Acid value and hydroxyl value each went through a minimum in the middle fractions (mol wt about 10³–10⁴), whereas the polyester–monoacid ratio increased with the molecular weight of the fraction. Cured films from alkyds with larger colloidal fractions gave better thermomechanical properties. The high mol wt colloidal fractions were preferentially adsorbed by pigment particles and thus stabilize the pigment dispersion in the coating formulation.

Principles for the Designing of Alkyd Resins

The process of alkyd resin designing should begin with the question, "What are the intended applications of the resin?" The application dictates property requirements, such as solubility, viscosity, drying characteristics, compatibility, film hardness, film flexibility, acid value, water resistance, chemical resistance, and environmental endurance. With the targets in mind, a selection of oil length and a preliminary list of alternative choices of ingredients can then be made. For commercial production, the raw material list is screened based on considerations of material cost, availability, yield, impact on processing cost, and potential hazard to health, safety, and the environment. The list may be further narrowed by limitations imposed by the production equipment or other considerations. Once the oil length and ingredients are chosen, the first draft of a detailed formulation for the resin can be made.

Predictive equations aimed at optimizing formulations for alkyd resins (26–28) provide only a first approximation of a starting formula because of the complexities of alkyd resin systems: formation of intramolecular cyclic structures, which reduce the chance of gelation; etherification of polyols, which increases the chance of gelation by forming higher functionality materials and reducing the number of hydroxyl groups available for esterification; cross-linking between unsaturated groups, especially conjugated double bonds, which increases the chance of gelation; and the phenomenon of microgel formation.

Except when nondrying alkyds are used strictly as plasticizers for other thermoplastic polymers, alkyd resins do not remain thermoplastic in their ultimate applications. The film integrity is largely derived after the resin molecules have been cross-linked, either through the unsaturation functionalities on their fatty acid side chains, or through the reactions of their residual hydroxyl or carboxyl functionalities with such cross-linking agents as amino resins or polyisocyanate materials. In a sense, alkyds are usually made and applied as "B-stage" resins. Therefore, it is not necessary to build the molecules of alkyd resins to huge molecular weights, as one would for thermoplastic polymers. In fact, too high a molecular weight leads to poor solubility and high solution viscosity, and is undesirable for practical applications. Most published data show that the number average molecular weight of alkyds is less than 10,000. Nevertheless, within practical limits, it is still preferable to have a linear backbone structure and high molecular weight to give the best film-forming and film properties. Alkyd formulations with an equimolar ratio of dibasic acids and polyols tend to have the best chance of achieving a linear molecular structure and high molecular weight.

Thus a simple molecular approach is favored by some alkyd chemists for deriving a starting formulation. The basic premise of this approach is that when the total number of moles of the polyols is equal to or slightly larger than that of the dibasic acids, and the hydroxyl groups are present in an empirically prescribed excess amount, the probability of gelation is very small. Table 7 lists the empirical requirements for excess hydroxyl groups at various oil (fatty acid) lengths of the alkyd. The values were developed empirically (27), primarily with PE alkyds; it has also been found to be satisfactory when other polyols are involved. With the new understanding that some of the hydroxyl groups are buried in microgel structures (19–25), such requirements may be better rationalized. The following examples illustrate this method for formulating alkyd resins.

Table 7. Excess Hydroxyl Content Required in Alkyd Formulations

Oil length, fatty acid, ° a	Excess OH based on diacid equivalents, ° o
62 or more	0
59–62	5
57–59	10
53–57	18
48–53	25
38–48	30
29–38	32

a Based on C18 fatty acids with average eq wt of 280. If the average eq wt of the monobasic acids is significantly different, adjustment is necessary.

Formulation of a 50% soya oil alkyd for baking enamels. The preliminary selection of ingredients includes alkali refined soya oil, phthalic anhydride (PA), and pentaerythritol. The basis for calculation is 1 mol of PA. From Table 7, the excess OH recommended at 50% oil length is 25%. Therefore, the quantity

of PE required, in equivalents is

$$E_{PE} = 1 \times 2 \times (1 + 0.25) = 2.5 \text{ eq} = 0.625 \text{ mol}$$

Because the total polyol is to be equimolar to PA, the glycerol from the soya oil must therefore be 0.375 mol, which gives 1.125 mol of soya fatty acids. Summarizing thus far:

Ingredient	Moles	[COOH], eq	[OH], eq	Weight, g
PA	1.0	2.000		148.0
soya oil	0.375	1.125	1.125	330.0
tech-PE	0.625		2.500	88.5
<i>Totals</i>	<i>2.0</i>	<i>3.125</i>	<i>3.625</i>	<i>566.6</i>
water	1.0			18.0
resin				548.5

This formulation does not meet the test of 50% oil length; the oil content must be reduced. A reduction in oil causes a corresponding reduction in glycerol, consequently, free glycerol is added to make up the loss. If $M_{PE} = x$, $M_{Gly} = y$, and $M_{oil} = z$ and total polyols is to be equimolar to dibasic acids, then $x + y + z = 1$. The 25% excess OH requirement can be expressed as

$$4x + 3y = 2.5$$

The 50% oil length requirement gives:

$$880z = (148 + 141.6x + 93y + 880z - 18) \times 0.5$$

where 880, 148, 141.6, and 93 are the mol wt of the oil, PA, PE, and glycerol, respectively.

Solving the simultaneous equations gives

$$x = 0.221, y = 0.539, \text{ and } z = 0.240$$

Thus, the "experimental" formulation is

Ingredient	Moles	[COOH], eq	[OH], eq	Weight, g
PA	1.0	2.000		148.0
soya oil	0.240	0.720	0.720	211.2
glycerol	0.539		1.617	50.1
tech-PE	0.221		0.884	31.3
<i>Totals</i>	<i>2.0</i>	<i>2.720</i>	<i>3.221</i>	<i>440.6</i>
water	1.0			18.0
resin				422.6

This formulation meets all of the requirements of the resin design, ie, equimolar PA and polyols, 25% excess OH, and 50% oil.

Formulation of a 50% TOFA alkyd for baking enamels. Assuming that PA, PE, ethylene glycol (EG), and refined TOFA with 4% rosin acids are the chosen ingredients, from the given constraints, the following simultaneous equations can be established:

$$M_{EG} = x, M_{PE} = y, \text{ and } M_{TOFA} = z$$

$$x + y = 1$$

$$2x + 4y = 2 \times (1 + 0.25) + z$$

$$295z = [148 + 141.8y + 62x + 295z - 18(1 + z)] \times 0.5$$

Solving the equations gives

$$x = 0.362, y = 0.638, \text{ and } z = 0.776.$$

Therefore, the experimental formulation is

Ingredient	Moles	[COOH], eq	[OH], eq	Weight, g
PA	1.0	2.00		148.0
tech-PE	0.638		2.552	90.3
EG	0.362		0.724	22.4
TOFA-4	0.776	0.776		228.9
<i>Totals</i>	<i>2.776</i>	<i>2.776</i>	<i>3.276</i>	<i>489.6</i>
water	1.776			(32.0)
resin				457.6

% excess OH = $(3.276 - 2.776) \times 2 = 25\%$, and, oil length = $228.9 / 457.6 = 50\%$ TOFA

These "experimental" formulations derived in the foregoing examples are only meant to be the starting formulations and must be fine-tuned based on small scale laboratory experiments before use in plant production.

The alkyd reaction is usually carried to a point short of completion, ie, to a point where the reaction mixture still shows a finite acid number. One reason for this practice is that the esterification reaction rate becomes very slow as the concentration of carboxyl groups becomes small, and it would be very time consuming to wait for the last residual carboxyl groups to react. Another reason is to guard against premature gelation, since the molecular chain length or the degree of polymerization is a function of the extent of the reaction as shown in equation 1. The esterification of phthalic anhydride is slower and shows higher temperature dependence, ie, higher activation energy, than that of fatty acids (29–31). Therefore, it is assumed that residual acidity is from unreacted dibasic acids; this contributes to the limiting of chain growth. In real practice, an additional safety margin against premature gelation is provided by having a slight molar excess of polyols over dibasic acids in the alkyd formulation. If the molar ratio between the polyols and the dibasic acids is r , equation 1 may be rewritten as:

$$x_n = (1 + 1/r)^{-(2-r)(1-p) + 1 - 1/r}$$

(2)

which indicates that a fractional increment in r and or a fractional reduction in p would give a substantial reduction in ∞_n . Generally, the value of r is chosen between 1 and 1.05.

Chemical Procedures for Alkyd Resin Synthesis

Different chemical procedures may be used for the synthesis of alkyd resins. The choice is usually dictated by the selection of the starting ingredients.

Alcohololysis Process. Cost and availability often dictate that oil, rather than free fatty acids, be used as the raw material for alkyd synthesis. Since oil, in the form of triglycerides, is essentially inert and does not participate in the polyesterification reaction, heating the oil with the polyol and the dibasic acid results in the formation of seedy polycondensates between the polyol and the polybasic acids leaving the oil unreacted. The two phases thus are incompatible. Therefore, the triglycerides must first react with additional polyol to redistribute the fatty acids among all of the polyols, thereby liberating free hydroxyl groups from the oil for further reaction with the dibasic acids. The reaction is *alcohololysis*. It is usually catalyzed by basic compounds such as metal oxides, hydroxides, salts or soaps such as naphthanates. In the past, litharge was the most popular choice as the catalyst. On a molar basis, lead compounds were found to be the most efficient among 36 compounds studied (32). In recent years, due to the concern of lead poisoning from the resultant coatings, lithium hydroxide, sodium hydroxide, or calcium oxide have been commonly used. The dosage of these catalysts is usually 0.01–0.06% metal based on the weight of the oil for lead, and 0.008–0.02% for lithium or calcium. The amount of catalyst added should be kept at the minimum required for completing the reaction in an acceptable batch time. Catalysts may cause poor color, poor water resistance, or haziness in the final resin.

Ideally, two moles of polyol react with one mole of triglyceride to form three moles of monoester. In reality, the reaction reaches an equilibrium, whereby some amount of di- and tri-esters and neat polyol, including glycerol and the added polyol, coexist in the reaction mixture. The compositions of the alcohololysis products at equilibrium from soya oil and glycerol (1:2 mole ratio), and soya oil and monopentaerythritol have been reported (33) as follows:

Component	Oil Glycerol, mol %	Oil Mono-PE, mol %
glycerol monoester	42	20.6
diester	21	6.2
triester	3	2.0
free glycerol	33	14.0
PE monoester		29.0
PE diester		16.8
PE triester		5.1
PE tetraester		negligible
free PE		6.3

Diols, such as ethylene glycol, are usually not added during the alcohololysis step because their monoesters have only one remaining hydroxyl group, and would function as chain stoppers, thus severely limiting their utility in the structure design of the resin molecules.

In general practice, the oil is first heated to about 230–250°C under an inert gas blanket and with agitation. The catalyst, usually predispersed in a small quantity of the oil, and the polyol, usually at two times the molar quantity of the oil present in the reactor, are added. The batch is reheated and maintained at the desired temperature, usually 230–250°C. The progress of the reaction is monitored by periodical sampling from the reactor and checking miscibility with anhydrous methanol. Triglycerides are not soluble in methanol, whereas monoglyceride is. When a volume of the alcoholysate can tolerate three or more volumes of methanol without becoming turbid, the alcohololysis process is considered complete.

Acidic contaminants are poisonous to the alcohololysis catalysts and must be avoided. If the oil has a high acid number, or there are high acidity residues left in the reactor from the previous batch, such as sublimed phthalic anhydride condensed under the dome of the reactor, the reaction can be severely retarded. A longer batch time or additional amount of catalyst is then required. Both are undesirable.

When the alcohololysis step is complete, the polybasic acid(s) and the balance of polyol, if any, are added. The batch is reheated and maintained at about 250°C to carry out the polycondensation step to the desired endpoint, usually a combination of the acid value and viscosity of the resin.

Fatty Acid Process. When free fatty acids are used instead of oil as the starting component, the alcohololysis step is avoided. All of the ingredients can therefore be charged into the reactor to start a batch. The reactants are heated together, under agitation and an inert gas blanket, until the desired endpoint is reached. Alkyds prepared by the fatty acid process have narrower molecular weight distribution and give films with better dynamic mechanical properties (34).

A modified form of the fatty acid process, dubbed the "high polymer alkyd technique" has been reported (35). A portion of the fatty acids is withheld in the first stage of the process to allow polycondensation between the dibasic acid and the polyol to have a better chance of extending the polyester chain without being terminated by monoacids. After the acid value of the reactant has reached a desired low level, indicating the completion of the polycondensation, the remaining portion of fatty acids is then added to complete the process. The resins prepared by this technique have a more linear backbone chain structure, higher molecular weight, and higher viscosity, as compared to the corresponding ones with identical formulation, but prepared by the conventional process.

Fatty Acid–Oil Process. When oil represents only a minor portion (1/3 or less) of the total furnish of fatty acids in an alkyd formulation, the alcohololysis step may be avoided. All of the ingredients, dibasic acid, polyol, oil, and free fatty acids, may be charged together into the reactor as in the fatty acid process. Apparently, the oil is incorporated into the resin by ester-interchange at the reaction temperature. The resultant resins give higher viscosity (4), faster surface drying, and slower through-dry (3). If the oil content is too high, not enough of it may be incorporated in time, resulting in a partial gelation to form "seeds."

Acidolysis Process. Isophthalic and terephthalic acids are difficult to process in ordinary alkyd preparation methods due to their high melting point and low solubility in the reaction mixture. An *acidolysis* process has been developed for this purpose (6). The dibasic acid is heated together with the oil in the resin formulation under agitation and an inert gas blanket to about 280°C, holding for about 40 min. In this reaction, which is self-catalyzed by the acidity of the reaction mixture, an ester interchange occurs. A carboxyl group of the dibasic acid displaces that of a fatty acid on the oil molecule and splits off the fatty acid. The completeness of the acidolysis reaction is determined by a tedious extraction of the oil phase and analysis of its free fatty acid content by titration. The analysis takes several hours to complete. Rapid test methods, comparable to the methanol miscibility test for alcohololysis, that could be used for process control of the acidolysis reaction have yet to be developed. Therefore, the process is normally controlled by reaction time and temperature, based on experience. After acidolysis, the reactant temperature is dropped to about 230°C, the polyol is charged and heated to the desired temperature to bring the esterification step to the desired endpoint. The acidolysis process is not suitable for phthalic anhydride or other dibasic acids with a high tendency to sublime.

Alkyd Resin Production Processes

Depending on the requirements of the chemical procedure, the processing method may be varied with different mechanical arrangements to remove the by-product, water, in order to drive the esterification reaction toward completion.

Fusion Process. In the fusion process, also frequently referred to as fusion cook, inert gas is continuously sparged from the bottom of the reactor to carry away water vapor from the reaction mixture. The exhaust is then either vented away or sent to a fume scrubber, which is frequently a small vessel with water atomizing nozzles. After the reaction is completed, the finished resin may be discharged, filtered, and packaged without solvent. More frequently, it is cooled to a safe temperature, then dissolved in the desired type and amount of solvent in a thinning tank, filtered, and packaged, or pumped

to a storage tank. The reactor usually needs to be cleaned by charging a small volume of solvent into the vessel and heating to reflux for an appropriate time period. If deemed necessary, the vessel is further cleaned by digestion with caustic soda solution.

The fusion process has the advantage of simplicity in mechanical arrangement. However, it has several significant disadvantages: Low boiling and or subliming ingredients, such as glycols and phthalic anhydride, are lost during the reaction causing production composition and properties to deviate from the design. The material loss causes an increase in the cost of the resin. Reactants as well as the product may adhere to the reactor walls above the surface level of the charge; this contamination may even act as a catalyst poison to subsequent batches. The resin produced from a fusion cook is more prone to develop dark colors. For these reasons, most manufacturers have discontinued the practice of fusion cook unless it is dictated by the existing equipment.

Solvent Process. In the solvent process, or solvent cook, water formed from the reaction is removed from the reactor as an azeotropic mixture with an added solvent, typically xylene. Usually between 3 to 10 wt % of the solvent, based on the total charge, is added at the beginning of the esterification step. The mixed vapor passes through a condenser. The condensed water and solvent have low solubility in each other and phase separation is allowed to occur in an automatic decanter. The water is removed, usually to a measuring vessel. The amount of water collected can be monitored as one of the indicators of the extent of the reaction. The solvent is continuously returned to the reactor to be recycled. Typical equipment for this process is shown in Figure 2. The reactor temperature is modulated by the amount and type of refluxing solvent. Typical conditions are:

Solvent	Wt %	Temperature °C
xylene	3	251–260
xylene	4	246–251
xylene	7	204–210
hiflash naphtha	10	204–210

The solvent vapor also serves as a blanket in the reactor. The processing solvent is usually left in the product as part of the dilution solvent.

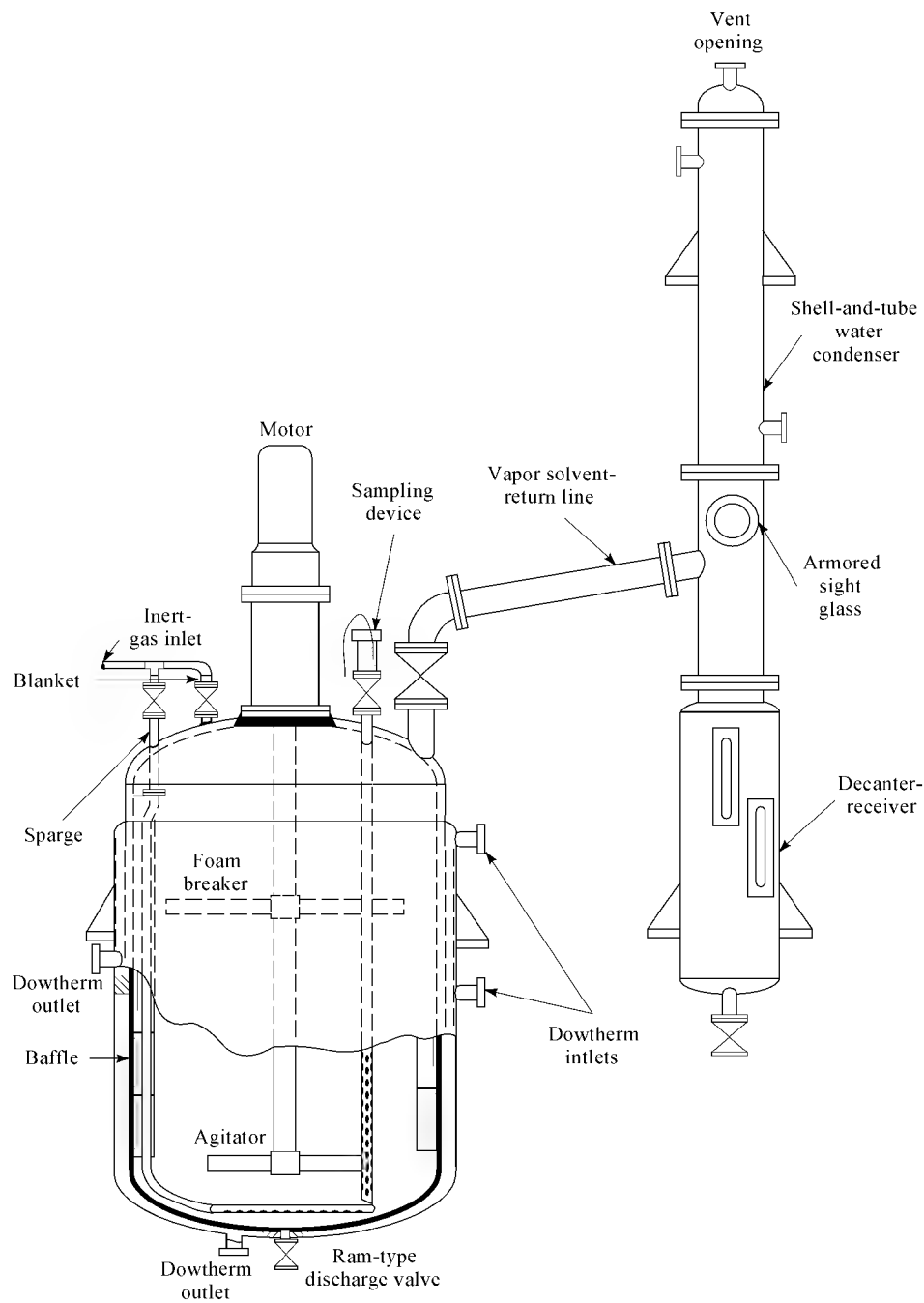


Fig. 2. Equipment for solvent processing of alkyd resins.

The refluxing solvent provides a constant wash to the reactor and brings back reactants that had escaped from the reaction mixture. The reaction temperature is better controlled by the constant refluxing, and the viscosity of the reaction mixture is lower, which improves the effectiveness of the agitation. The product usually has better color and is more uniform than material made by the fusion process. Ordinarily, the reactor requires no more than

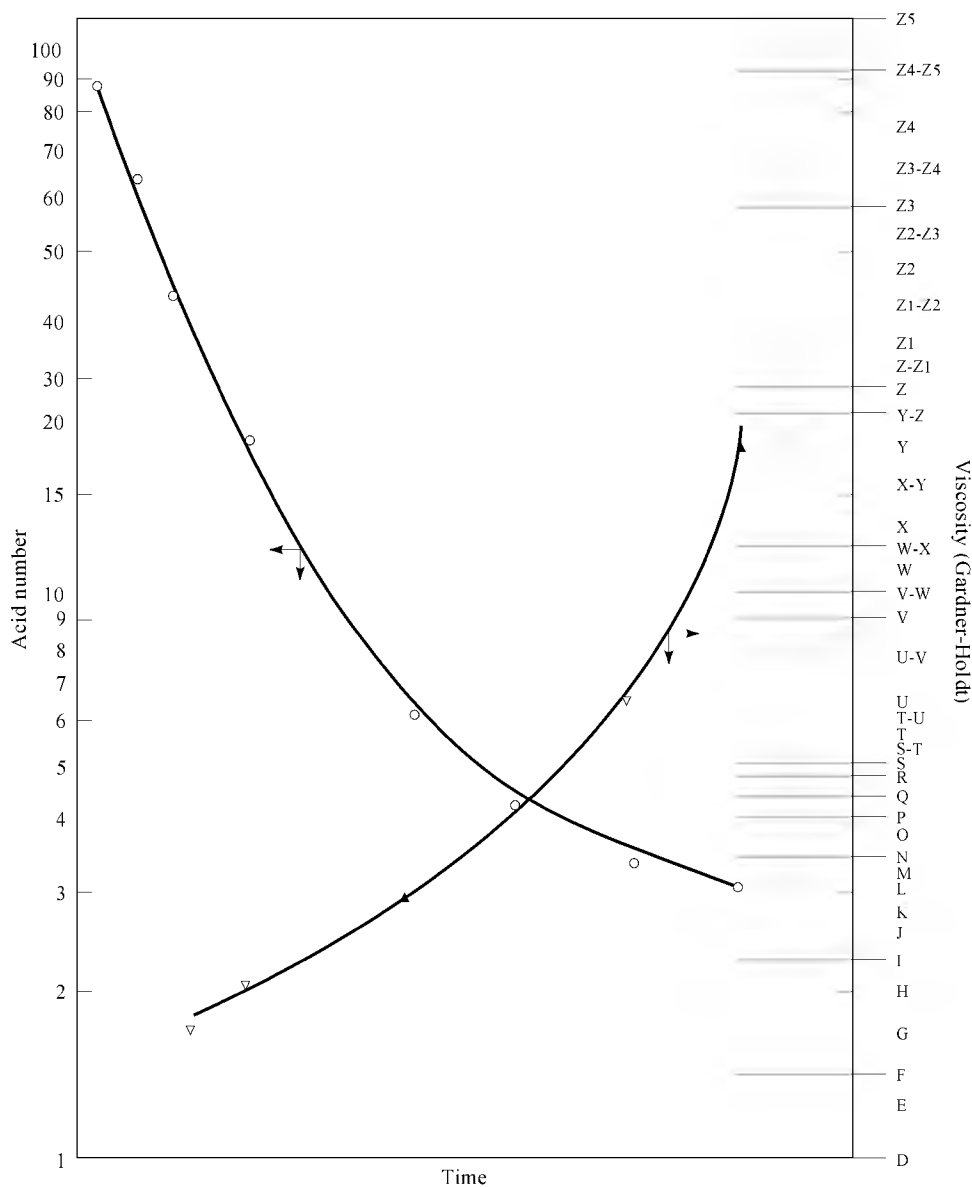


Fig. 4. Alkyd reaction control plots.

Safety and Environmental Precautions

The manufacturing of alkyd resins involves a wide variety of organic ingredients. Whereas most of them are relatively mild and of low toxicity, some, such as phthalic anhydride, maleic anhydride, solvents, and many of the vinyl (especially acrylic) monomers, are known irritants or skin sensitizers and are poisonous to humans. The hazard potential of the chemicals should be determined by consulting the Material Safety Data Sheets provided by the suppliers, and recommended safety precautions in handling the materials should be practiced. Personal safety equipment such as protective goggles, gloves, clothing, and respiratory devices should be used. Since large quantities of highly flammable solvents are routinely handled in an alkyd plant, fire safety must be observed. Electrical equipment and power circuitry in the plant should conform to all applicable codes, and all equipment should be properly grounded. The areas for the reactors and storage tanks should be separated by fire walls, and must be adequately ventilated. Storage tanks should be blanketed by inert gas. A slight positive pressure of inert gas should be maintained in the reactor or storage tanks during the discharging of the resin or resin solution to prevent air from being sucked into the vessel to form an explosive mixture with the solvent vapor.

With the ever increasing awareness of the need of environment protection, the emission of solvent vapors and organic fumes into the atmosphere should be prevented by treating the exhaust through a proper scrubber. The solvent used for cleaning the reactor is usually consumed as part of the thinning solvent. Aqueous effluent should be properly treated before discharge.

Modification of Alkyd Resins by Blending with Other Polymers

One of the important attributes of alkyds is their good compatibility with a wide variety of other coating polymers. This good compatibility comes from the relatively low molecular weight of the alkyds, and the fact that the resin structure contains, on the one hand, a relatively polar and aromatic backbone, and, on the other hand, many aliphatic side chains with low polarity. An alkyd resin in a blend with another coating polymer may serve as a modifier for the other film-former, or it may be the principal film-former and the other polymer may serve as the modifier for the alkyd to enhance certain properties. Examples of compatible blends follow.

Nitrocellulose based lacquers often contain short or medium oil alkyds to improve flexibility and adhesion. The most commonly used are short oil nondrying alkyds. Amino resins or urethane resins with residual isocyanate functional groups may be added to cross-link the coating film for improved solvent and chemical resistance. The principal applications are furniture coatings, top lacquer for printed paper, and automotive refinishing primers.

Amino resins (qv) are probably the most important modifiers for alkyd resins. Butylated urea-formaldehyde or melamine-formaldehyde resins are compatible with alkyds. They react with the free hydroxyl groups of the alkyd to effect cross-linking, and to impart hardness, mar resistance, chemical resistance and durability to the coating. Short or medium oil alkyds of both drying and nondrying types are frequently used. Color and color retention requirements often dominate the choice of the alkyd. Many industrial baking enamels, such as those for appliances, coil coatings, automotive finishes (especially refinishing enamels) are based on alkyd-amino resin blends. Some of the so-called catalyzed lacquers for finishing wood substrate require very low bake or no bake at all.

Chlorinated rubber is often used in combination with medium oil drying type alkyds. The alkyd gives better toughness, flexibility, adhesion, and durability, and the chlorinated rubber contributes to faster drying and better resistance to water and chemicals. The principal applications are highway traffic paint, concrete floor, and swimming pool paints.

Vinyl resins, ie, copolymers of vinyl chloride and vinyl acetate which contain hydroxyl groups from the partial hydrolysis of vinyl acetate and or carboxyl groups, eg, from copolymerized maleic anhydride, may be formulated with alkyd resins to improve their application properties and adhesion. The blends are primarily used in making marine top-coat paints.

Synthetic latex house paints sometimes contain emulsified long oil or very long oil drying alkyds to improve adhesion to chalky painted surfaces.

Silicone resins with high phenyl contents may be used with medium or short oil alkyds as blends in air-dried or baked coatings to improve heat or weather resistance; the alkyd component contributes to adhesion and flexibility. Applications include insulation varnishes, heat-resistant paints, and marine coatings.

Chemically Modified Alkyd Resins

Although blending with other coating resins provides a variety of ways to improve the performance of alkyds, or of the other resins, chemically combining the desired modifier into the alkyd structure eliminates compatibility problems and gives a more uniform product. Several such chemical modifications of the alkyd resins have gained commercial importance.

Vinylated Alkyds. These are alkyd resins that have incorporated a significant amount (20–60% by weight) of vinyl monomers, such as styrene, vinyl-toluene, methyl methacrylate, etc, by grafting the monomers through a free radical mechanism onto unsaturated reaction sites in the resin molecules. The modified resin embodies the good attributes of ease of application, good wetting, and adhesion from the alkyd, and fast solvent release, hardness, and weather resistance from the vinyl modification. The common objective of such a modification is to achieve a "drying" rate comparable to that of lacquer materials. The reaction sites on alkyd resin molecules are primarily the allylic carbons on unsaturated fatty acid chains, and the double bond of α,β-unsaturated dibasic acids. Free radicals, generated from the thermolysis of such free radical initiators as benzoyl peroxide, dicumyl peroxide, di-*t*-butyl peroxide, etc, are usually required to initiate the reaction. Ideally, the initiating species attacks the active sites on the resin molecules and all of the added monomers are evenly distributed in grafted side chains. In reality, part of the monomers engage in homopolymerization, and some of the resin molecules remain unmodified. The presence of a large amount of homopolymer of the vinyl monomer leads to incompatibility and results in a lazy product. Methods that have been used to minimize homopolymerization include using fatty acids with conjugated diene structures, using maleic anhydride as part of the dibasic acids for the alkyd, choosing initiators such as peroxides or hydroperoxides that tend to extract allylic protons rather than to add to double bonds, avoiding initiators that decompose at very low temperatures, adding the monomer gradually along with an appropriate amount of the initiator, choosing monomers that have a more favorable tendency to copolymerize with the active species on the alkyd resin, and properly maintaining the reaction temperature. Chain transfer is the preferred mechanism for terminating the chain growth from the addition polymerization of the monomer. Usually the solvent, the fatty acid chain, and the monomer are effective chain transfer agents. If an additional transfer agent is used, care must be exercised to avoid formation of a large amount of very low molecular weight homopolymers, which results in poor film properties of the final product. Occasionally, vinylation is first performed on the fatty acids or the oil before the alkyd reactions.

The presence of a large amount of either conjugated fatty acids or maleic anhydride in the alkyd formulation gives rise to a high probability of premature gelation during the alkyd reaction. Allowance must be made in the alkyd formulation, and the polyesterification is frequently terminated at a relatively high acid number (about 15) to avoid gelation. The optimum amount of maleic anhydride in the alkyd is an amount having a maleic group in one-third of the resin molecules (18).

A common procedure for the preparation of vinylated alkyds is as follows. A base alkyd resin is brought to the desired endpoint. The resin is then cooled to about 160°C and often diluted with aromatic thinner. The desired monomer is added, usually at about 20–60% based on the final product, followed by an appropriate amount of a free radical initiator. Alternatively, a premix of the monomer and the initiator is added at a controlled rate over most of the reaction. The reaction is brought to monomer reflux, until the residual monomer content has fallen below a specified level. Residual monomer, if any, is stripped away before the product is diluted in a solvent, filtered, and packaged.

Silicone Alkyds. These resins are etherification products of alkoxy polysiloxane oligomers and the free hydroxyl groups of alkyd resins (36,37). The property improvements and applications are similar to those of the alkyd-silicone blends, with the added advantage of incorporating the stable Si—O—C structure into the alkyd molecules. The preferred silicone oligomers are those with high phenyl contents, and the alkyds at long or medium oil length based on polyols with primary hydroxyls. The etherification reaction may be carried out on an alkyd resin designed for the purpose, or on the polyol before it is used in alkyd preparation. The silicone content of the modified alkyd lies usually between 20 and 60% of the total product. For moderate service temperature requirements, isophthalic alkyds rather than the phthalic type can be used to augment the thermal stability imparted by silicone modification.

Urethane Alkyds. Uralkyds are alkyds with a part or even all of the dibasic acids replaced by diisocyanates. The isocyanate group, N=C=O, reacts with the hydroxyl group of a polyol, at low temperature, to form a urethane linkage, —NHCO— without forming water as a by-product (see URETHANE POLYMERS). Toluene diisocyanate [584-84-9], TDI, is commonly used for such modification. Since the NCO group is very reactive with labile protons, water must be excluded from the reaction system. The esterification reaction of the base alkyd must be brought to the desired endpoint with the by-product water removed, and the temperature lowered to about 100°C to prevent any continuation of the esterification before the introduction of the NCO reactant. TDI is highly toxic and is usually handled in a closed system under a dry inert gas blanket. Metallic soaps, such as dibutyltin dilaurate, stannous octoate, or calcium naphthanate, are used as reaction catalysts. The reaction is vigorous and exothermic. Therefore, the reaction temperature is maintained under 135°C and great care must be exercised to bring the reaction under proper control.

Uralkyds have superior adhesion, hardness, abrasion resistance, durability, and chemical resistance to the unmodified alkyds. They find applications in wood floor finishes, marine coatings, metal primers, and maintenance paints.

Phenolic Alkyds. Phenolic resins (qv), are well known for their contribution in improving the hardness, gloss, and water and chemical resistance in oleoresinous varnishes. Those based on *p*-alkyl substituted phenols with heat-reactive methylol groups have also been incorporated into alkyd resins. The reaction has not been well studied. Presumably, the methylol group reacts with the unsaturation in the fatty acid chain to form the chroman structure, similar to what is believed to occur in varnish. Etherification between the methylol group and free hydroxyl of the alkyd resins, catalyzed by the residual acidity in the resin, is another possible reaction.

Polyamide Alkyds. Modification of alkyds with polyamides produces a special rheological behavior—the alkyds are thixotropic (39,40). Typically, the polyamide resin is based on dimer acids (qv), ie, dimerized unsaturated fatty acids, and aliphatic diamines such as ethylenediamine. These react to form polyamide resins with low acid and amine values. The alkyd resin is a medium or long oil drying alkyd. The reaction products from the polyamide and the alkyd are gel-like materials which undergo a time-dependent shear-thinning, and recover to the gel-like state after the shearing action is stopped. This allows the preparation of "no-drip" paints, which are easy to brush and can be applied at high film thickness from a single coat with little or no danger of sagging. Pigment settling during storage of the paint is also minimized. The principal applications are flat oil-based architectural paints and maintenance paints. Generally, up to 10% of the polyamide based on the weight of the alkyd is added to the alkyd and heated at normal alkyd reaction temperature under agitation. Ester interchange reactions take place, and fragments of the polyamide resin become chemically bonded to the alkyd. The modified alkyd serves as a compatibilizer for the mutually insoluble unreacted polyamide and alkyd to form a gel-like structure. The stiffness of the structure decreases with the increasing amount of the compatibilizer. If the reaction is allowed to continue and there is no unreacted polyamide left in the system, little or no thixotropy is exhibited. Therefore, the reaction must be precisely controlled to give the desired degree of thixotropy. Aromatic solvents such as xylene tend to destroy the thixotropic structure. Therefore, they must be reduced to less than 0.5% in the product. Polyamide modified alkyd resins are available commercially to be used as additives for making thixotropic alkyd paints.

High Solids Alkyds

There has been a strong trend in recent years to increase the solids content of all coating materials, including alkyds, to reduce solvent vapor emission. In order to raise solids and still maintain a manageable viscosity, the molecular weight of the resin must be reduced. Consequently, film integrity must be developed through further chain extension and or cross-linking of the resin molecules during the "drying" step. A high cross-linking density necessitated by the lower molecular weight of the resin builds high stress in the film and causes it to be prone to cracking. Therefore, adequate flexibility should be

designed into the resin structure. This means that the distance between the hydroxyl groups of the polyol and the carboxyl groups of the dibasic acid must be lengthened by linear linkages. Thus, long chain diols, polyether polyols, and linear α,ω -dibasic acids not only build in more flexibility but also reduce the viscosity for high solids alkyds due to the greater spacing of polar ester groups and the reduction of aromaticity in the resin structure. In addition to the manipulation of resin molecular structure for increasing coating solids, the use of "reactive diluents" is another approach that has been actively explored. A reactive diluent is a material that has low volatility and can function as a solvent or diluent to reduce the viscosity of a coating composition, but has functional group(s) that can participate in the drying mechanism and become an integral part of the film. Thus, drying oils and simple esters of highly unsaturated fatty acids have been used as low cost reactive diluents for alkyd resins. However, they have limitations in compatibility, viscosity, and drying rate. Vernonia oil, a naturally occurring vegetable oil with both epoxy and unsaturation functionalities reportedly has broad compatibility with alkyds at various oil lengths (41). Vinylic monomers have been synthesized and tested as reactive diluents for air or force drying alkyds (42–45). Another alternative, though with very limited capacity for increasing the solids content of alkyd based coatings, is the use of more active oxygenated solvents to reduce the viscosity of resin solutions.

Chain extension and cross-linking of high solids alkyd resins are typically achieved by the use of polyisocyanato oligomers or amino resins. An adequate amount of excess hydroxyl groups must be designed into the alkyd structure to provide reaction sites for these modifiers. In order to limit the molecular weight of the alkyd resin, the molar ratio between polyols and dibasic acids should be greater than one. The hydroxyl functionality of the formulation should be controlled by a careful selection of polyols to avoid an over-presence of free hydroxyl groups in the product, which would adversely affect water resistance and other properties of the coating film. Most of the high solids alkyd systems are used in industrial baking finishes. The market for high solids alkyds in air drying gloss and semi-gloss architectural enamels is growing, especially in California. Higher doses of driers are usually needed to achieve acceptable drying rates (46).

Water-Reducible Alkyds

Replacing solvent-borne coatings with water-borne coatings not only reduces solvent vapor emission, but also improves the safety against the fire and health hazards of organic solvents. Alkyd resins may be made water-reducible either by converting the resin into an emulsion form or by incorporating "water-soluble" groups in the molecules.

The most common approach for imparting water solubility to an alkyd resin is to provide free pendent carboxyl groups in the resin and neutralize them with a fugitive base, such as ammonia or low molecular weight amines, to build ionic characteristics into the resin. Nonfugitive base materials, such as caustic soda, leave the salt in the coating film and damage its water and corrosion resistance. Trimellitic anhydride (TMA) is the most frequent ingredient chosen to provide the pendent carboxyl groups.

In the recommended procedure (7) for the preparation of water-soluble alkyds TMA is not added in the initial stage of the alkyd reaction so that its high functionality does not cause gelation. When the reaction has progressed to a desired low acid number, ie, the building of the polymer chain is completed, the temperature is lowered to 180°C, the TMA is then added and maintained at that temperature until a desired acid number, usually about 50–60, is reached. At such a temperature, only the anhydride group of the TMA reacts to form half-esters, and the remaining two carboxyl groups remain essentially unreacted. If it is desirable to have the TMA in the backbone structure of the resin, a part of the TMA is charged in the beginning of the alkyd reaction, often with an appropriate amount of a monohydric alcohol, such as benzyl alcohol, to balance the functionality of the system. The remaining TMA is then added in the same manner as described previously to "end-cap" the resin and to give the pendent carboxyl groups for "water solubilization."

The finished resins are usually dissolved in oxygenated coupling solvents, such as glycol ethers, to improve the solubilization of the resin in aqueous media and the handling of the resin. Water and the base are premixed and added to the resin solution when needed. The coupling solvents usually have higher boiling points than water. During the drying process, the solvent is enriched in the coating film as water evaporates preferentially. The resin molecules become better solubilized, ie, molecular chains are extended, and result in better formation and integrity of the film. As expected, water-reducible alkyds suffer from limited hydrolytic stability. Therefore, they are primarily used in industrial coatings. A considerable improvement in package stability, from the current 3–4 months to 1–2 yr, would be needed in order for water-reducible alkyds to be viable in trade sale paints. Steric shielding and avoidance of neighboring nucleophiles to the ester groups in the resin are two of the conditions for the attainment of maximum hydrolysis resistance for polymer ester groups (47). Partial esters of TMA are reportedly relatively stable at room temperature, but suffer substantial hydrolysis within a few weeks at elevated temperatures (48). However, they are more hydrolytically stable than partial esters of IPA or PA (49). Glycerol gives resins with poor hydrolytic stability (50), therefore, polyols with primary hydroxyl groups are preferred for the preparation of water-soluble alkyds.

Economic Aspects

Alkyd resins, as a family, have remained the workhorse of the coatings industry for decades. In the United States, the total consumption of alkyds (3,51,52) increased from about 200,000 t in the mid 1950s to over 300,000 t in the mid 1960s. Consumption peaked in 1973 at about 345,000 t constituting about one-third of all synthetic coating resins. In 1980, alkyds still accounted for 30% of the 1,090,000 t of all resins consumed for coatings. From 1987 through 1989, use continued at about 300,000 t per year, but market shares among all coating resins was reduced to 26% in 1987 and 25% in 1989. Of the 300,000 t consumed, about 40% each go into architectural coatings and industrial product finishes. Industrial forecasts show further decline for alkyds or show no growth in these markets. The remaining 20% of alkyds go into such specialty coating applications as traffic paints, auto refinishes, aerosol paints and others. Demand for alkyds in specialty coatings are expected to grow with the market, since they do not yet face the same constraint on VOC regulations. If the total alkyds consumed in recent years is classified by their dibasic acid component, about 50% belongs to the unmodified phthalic type, about 28% modified phthalic type, about 13% based on isophthalic, and the balance based on polybasic acids other than phthalic or isophthalic. The top alkyd resin manufacturers in the U.S. are Cargill, Reichhold, a subsidiary of Dainippon Ink & Chemicals, Inc., and Spencer Kellog, now a part of NL Industries, Inc. The median price (52,53), of general types of alkyd resin, solids base, was \$1.98 /kg in Nov. 1990 compared to about 44¢ in 1955, about 66¢ in 1975, and about \$1.54 in 1983, reflecting the increases in raw material cost.

Alkyd consumption in western Europe has also been on a gradual decline in recent years. Nevertheless, there was still about 345,000 t consumed in 1986. About 55% of it went to construction and architectural coatings.

The situation has been slightly different in Japan, the third major segment of the global market. Alkyd consumption in recent years has actually been increasing. It was reported at 154,000 t in 1987 with over 80% in industrial finishes (52).

Future Prospects. Because of the efforts of the coatings industry to reduce solvent emission, there has been a clear gradual decline in the market share of alkyds as a group relative to all synthetic coating resins. However, their versatility and low cost will undoubtedly maintain them as significant players in the coatings arena. Alkyds are much more amenable to development of higher solids compositions than most other coating resins. Great strides in the development of water-borne types have also been made in recent years. Another good reason to remain optimistic about alkyds for the future is that a significant portion of their raw material, fatty acids, is renewable.

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ALKYLATION

The alkylation described in this article is the substitution of a hydrogen atom bonded to the carbon atom of a paraffin or aromatic ring by an alkyl group. The alkylations of nitrogen, oxygen, and sulfur are described in separate articles (see AMINES; ETHERS).

Significant technological development has been made in the area of alkylation in recent years. Environmental concerns associated with mineral acid catalysts have encouraged process changes and the development of solid-bed alkylation processes. The application of heterogenous catalysts, especially zeolite catalysts, has led to new alkylation technologies. Research efforts to develop environmentally acceptable, economical technologies by applying new materials as alkylation catalysts will continue, and more new technologies are expected to be commercialized in the 1990s.

This article covers important industrial technologies and the direction of future technological development. The description of alkylation chemistry and conventional alkylation technologies covered in the earlier editions of this *Encyclopedia* and other references is minimized (1,2) (see also FRIEDEL-CRAFT'S REACTIONS).

Nomenclature

Open-chain saturated hydrocarbons have the generic names alkanes and paraffins. In this article, terms such as hexanes, heptanes, and octanes are synonymous with C₆, C₇, and C₈ alkanes, respectively, and do not refer to the straight chains of 6 carbons, 7 carbons, and 8 carbons, as defined in the IUPAC system.

The ending *ene* is adopted for straight-chain monounsaturated hydrocarbons. Thus, butenes refer to 1-butene and 2-butene. The ending *ylene* denotes a monounsaturated hydrocarbon that consists of the same number of carbons as expressed by the name; ie, butylenes are 1-butene, 2-butene, and isobutylene (methylpropene). The generic names alkenes and olefins refer to monounsaturated hydrocarbons.

The prefix *iso* is used loosely to denote branched alkanes or alkenes that have one or more methyl groups only as side chains.

Alkylation of Paraffinic Hydrocarbons

Paraffin alkylation as discussed here refers to the addition reaction of an isoparaffin and an olefin. The desired product is a higher molecular weight paraffin that exhibits a greater degree of branching than either of the reactants.

The principal industrial application of paraffin alkylation is in the production of premium-quality fuels for spark-ignition engines. Originally developed in the late 1930s to meet the fuel requirements of high performance aviation engines, alkylation is now primarily used to provide a high octane blending component for automotive fuels. Future gasoline specifications will continue to favor the clean-burning characteristics and the low emissions typical of alkylate. Alkylate production capacity was more than 50 million tons per year in 1989 and is expected to grow as worldwide gasoline specifications become more stringent.

CATALYSTS AND REACTIONS

Although the alkylation of paraffins can be carried out thermally (3), catalytic alkylation is the basis of all processes in commercial use. Early studies of catalytic alkylation led to the formulation of a proposed mechanism based on a chain of ionic reactions (4–6). The reaction steps include the formation of a light tertiary cation, the addition of the cation to an olefin to form a heavier cation, and the production of a heavier paraffin (alkylate) by a hydride transfer from a light isoparaffin. This last step generates another light tertiary cation to continue the chain.

In practice, the alkylate is a complex mixture of branched paraffins that cannot be explained solely by the chain mechanism. Since the 1960s, studies using more sophisticated experiments and analytical techniques have shown that a complex combination of parallel and sequential ionic reactions must be involved as well (7–11). Oligomerization to C₁₂₊ cations followed by scission and or hydride transfer can produce light and heavy ends as well as alkylate of the expected molecular weight. An alternative route to alkylate, especially with isobutylene feeds, is dimerization of feed olefins followed by hydride transfer. Isomerization of the feed olefin prior to alkylation is significant for the *n*-butenes. Hydrogen transfer, or self-alkylation, results in the production of isooctane and a light paraffin from two moles of isobutane and one mole of a light olefin. The relative extent of the various reactions depends on the catalyst as well as the feed olefin and operating conditions.

The catalysts used in the industrial alkylation processes are strong liquid acids, either sulfuric acid [7664-93-9] (H₂SO₄) or hydrofluoric acid [7664-39-3] (HF). Other strong acids have been shown to be capable of alkylation in the laboratory but have not been used commercially. Aluminum chloride [7446-70-0] (AlCl₃) is suitable for the alkylation of isobutane with ethylene (12). Super acids, such as trifluoromethanesulfonic acid [1493-13-6], also produce alkylate (13). Solid strong acid catalysts, such as Y-type zeolite or BF₃-promoted acidic ion-exchange resin, have also been investigated (14–16).

Sulfuric Acid Alkylation. The H₂SO₄ alkylation process was developed during the late 1930s. In the late 1980s, the H₂SO₄ process accounted for about 50% of the motor fuel alkylate produced worldwide.

The modern H₂SO₄ processes are differentiated primarily by the type of reactor system that is used. The reactor must generate a high degree of mixing of the two-phase system (hydrocarbons and H₂SO₄), provide efficient heat removal via refrigeration to keep temperatures in the range of 5–10°C, and provide sufficient time for completion of the reaction. Two reactor systems, the Stratco Contactor (17) and the Kellogg Cascade Reactor (18), account for most of the licensed operating capacity.

A simplified flow diagram of a modern H₂SO₄ alkylation unit is shown in Figure 1. Excess isobutane is supplied as recycle to the reactor section to suppress polymerization and other undesirable side reactions. The isobutane is supplied both by fractionation and by the return of flashed reactor effluent from the refrigeration cycle.

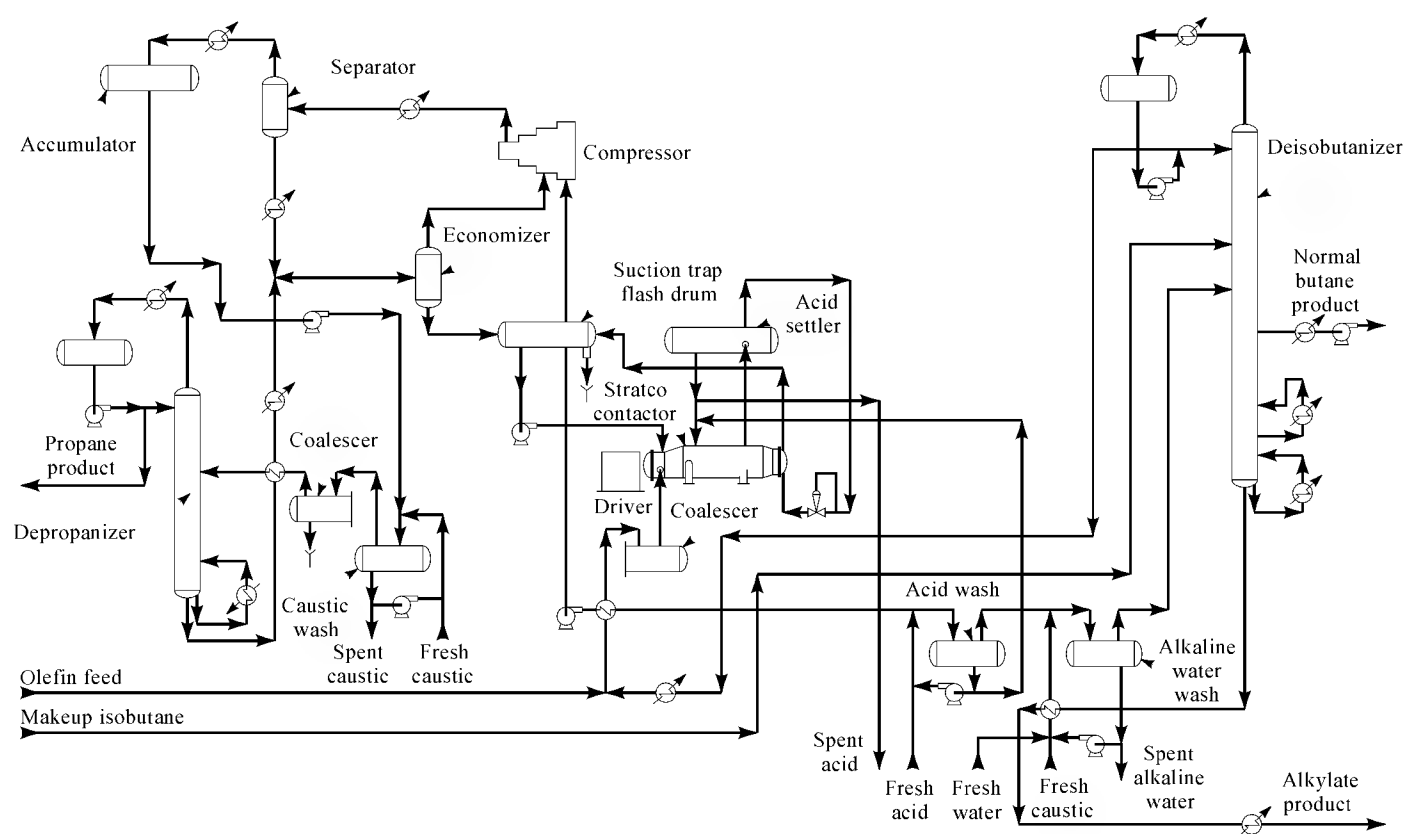


Fig. 1. H_2SO_4 alkylation unit with effluent refrigeration.

Courtesy of Stratco Inc.

Propane and light ends are rejected by routing a portion of the compressor discharge to the depropanizer column. The reactor effluent is treated prior to debutanization to remove residual esters by means of acid and alkaline water washes. The deisobutanizer is designed to provide a high purity isobutane stream for recycle to the reactor, a sidecut normal butane stream, and a low vapor pressure alkylate product.

The H_2SO_4 concentration is controlled above 90% to provide the optimum activity and selectivity. Purity is maintained by the withdrawal of system acid and replacement with fresh 98% acid. The spent acid is returned to an acid manufacturing plant for reprocessing.

HF Alkylation. The HF alkylation process was developed in the late 1930s and commercialized in the 1940s. Initially, the growth rate of capacity was lower than for H_2SO_4 , but by the 1980s, the capacity was approximately equivalent.

The modern HF alkylation processes are also differentiated primarily by the reactor system that is used. The Phillips process employs a gravity acid circulation system and a riser reactor (19). The UOP process uses a pumped acid circulation system and an exchanger reactor (20).

A simplified flow diagram of a modern HF alkylation unit is shown in Figure 2. Olefin feed and recycle isobutane are combined prior to contacting the acid catalyst in the reactor. Cooling water maintains the reactor temperature in the range of 20–40°C. Acid is settled from the reactor effluent and is returned to the reactor. The hydrocarbon phase is routed to the isostripper for fractionation into an isobutane recycle stream, a sidecut normal butane product, and an alkylate bottoms product. Propane is removed from the system by routing an overhead stream from the isostripper to the HF stripper. If the unit processes any significant quantity of propylene, a depropanizer is included to produce a high purity propane product.

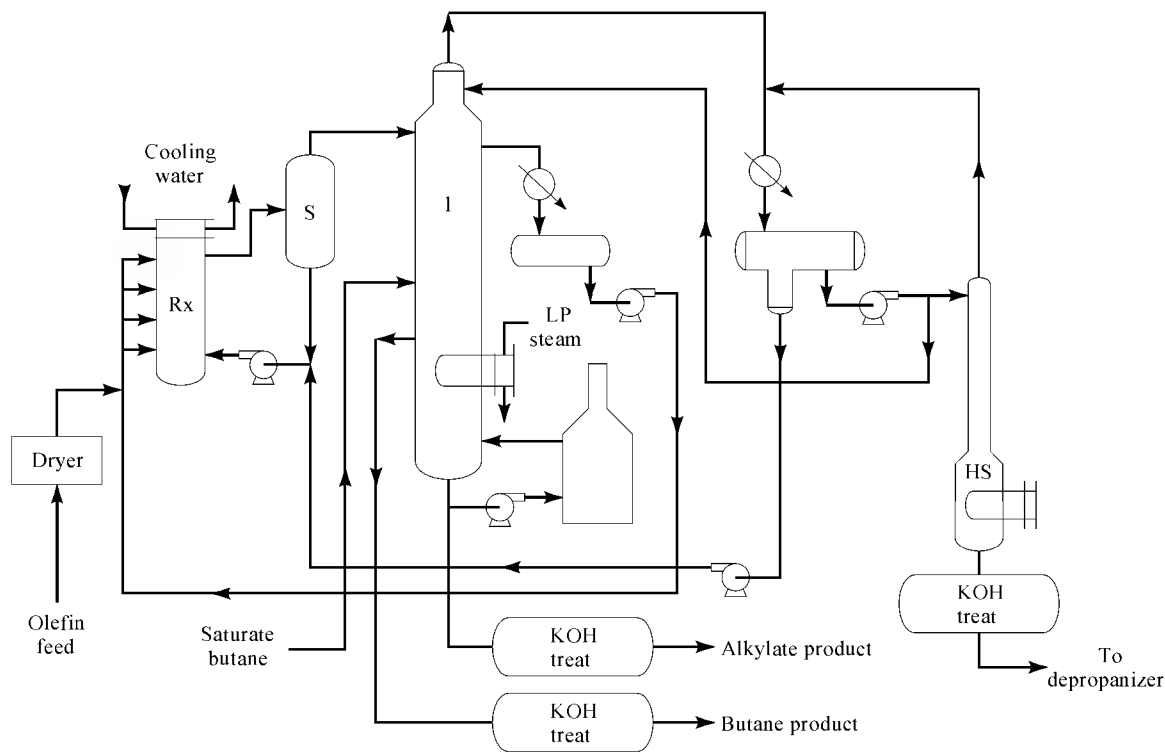


Fig. 2. UOP HF alkylation process with butylene feed: Rx reactor; S settler; I isostripper; HS HF stripper.

Before leaving the unit, the products are treated with potassium hydroxide to remove any trace acidity. In addition, any product streams that are

used for liquefied petroleum gas (LPG) are processed over alumina at elevated temperatures to remove residual organic fluorides.

The HF concentration of the acid catalyst is maintained in the range of 85–95° by regeneration within the unit's fractionation facilities. A separate acid regeneration column (not shown in Figure 2) is also included to provide a means to remove excess acid-soluble oils and water. The regeneration of acid in the unit accounts for the low consumption of fresh acid by the HF process.

FEEDSTOCK AND PRODUCTS

Isobutane. Although other isoparaffins can be alkylated, isobutane [75-28-5] is the only paraffin commonly used as a commercial feedstock. The hydrocarbon cracking operations that generate feed olefins generally do not produce sufficient isobutane to satisfy the reaction requirements. Additional isobutane must be recovered from crude oil or natural gas liquids or generated by other refinery operations. A growing quantity of isobutane is produced by the isomerization of *n*-butane [106-97-8].

Butylenes. Butylenes are the primary olefin feedstock to alkylation and produce a product high in trimethylpentanes. The research octane number, which is typically in the range of 94–98, depends on isomer distribution, catalyst, and operating conditions.

The effect of butene isomer distribution on alkylate composition produced with HF catalyst (21) is shown in Table 1. The alkylate product octane is highest for 2-butene feedstock and lowest for 1-butene; isobutylene is intermediate. The fact that the major product from 1-butene is trimethylpentane and not the expected primary product dimethylhexane indicates that significant isomerization of 1-butene has occurred before alkylation.

Table 1. HF Alkylation Products from Pure Butene Isomers^a

Alkylate product	Feed Isomer			
	1-Butene [106-98-9]	<i>trans</i> -2-Butene [590-18-1]	<i>cis</i> -2-Butene [624-64-6]	Isobutylene [115-11-7]
carbon number distribution, wt %				
C ₅	3.3	1.9	1.8	5.5
C ₆	1.7	1.5	1.5	3.1
C ₇	2.4	2.3	2.1	3.7
C ₈	85.0	91.4	91.8	80.1
C ₉₊	7.6	2.9	2.8	7.6
<i>total</i>	100.0	100.0	100.0	100.0
C ₈ H ₁₈ structural distribution, wt %				
trimethylpentanes	77.5	92.1	91.4	89.0
dimethylhexanes	22.1	7.9	7.8	11.0
methylheptanes	0.4		0.8	
estimated octane				
research—clear	94.4	97.8	97.6	95.4
motor—clear	91.6	94.6	94.4	93.4

^a Ref. 22.

The H₂SO₄ catalyst produces a high octane product of similar composition from either 2-butene or 1-butene. This fact suggests that the isomerization of 1-butene to 2-butene is more complete than in the HF system. Isobutylene produces a slightly lower product octane than do the *n*-butenes. The location of a methyl *tert*-butyl ether [1634-04-4] (MTBE) process upstream of the H₂SO₄ alkylation unit has a favorable effect on performance because isobutylene is selectively removed from the alkylation feed.

Propylene. Propylene alkylation produces a product that is rich in dimethylpentane and has a research octane typically in the range of 89–92. The HF catalyst tends to produce somewhat higher octane than does the H₂SO₄ catalyst because of the hydrogen-transfer reaction, which consumes additional isobutane and results in the production of trimethylpentane and propane.

Amylenes. Amylenes (C₅ monoolefins) produce alkylates with a research octane in the range of 90–93. In the past, amylenes have not been used widely as an industrial alkylation charge, although in specific instances, alkylation with amylenes has been practiced (23). In the future, alkylation with amylenes will become more important as limits are placed on the vapor pressure and light olefin content of gasolines.

FUTURE TECHNOLOGY TRENDS

Future technology developments in paraffin alkylation will be greatly influenced by environmental considerations. The demand for alkylate product will continue to increase because alkylate is one of the most desirable components in modern low emission gasoline formulations. Increased attention will be focused on improving process safety, reducing waste disposal requirements, and limiting the environmental consequences of any process emissions.

Hydrofluoric acid has long been recognized as a hazardous material that must be handled with care. However, in recent years concerns have increased over the possible consequences of an accidental release of HF. The results of a 1986 spill test showed that a large portion of the released HF can form a vapor cloud (24). In response to this information, the refining industry has acted to further tighten the already rigorous operating and design standards for HF plants. Periodic hazard reviews are being recommended for all operating units to ensure that the proper systems and procedures are in place (25). One test has shown that water spray systems can be an effective part of an overall program to mitigate the danger of an accidental spill (26).

Acid modifiers have been used to a limited extent to reduce acid consumption in the H₂SO₄ alkylation process (27). Increased catalyst costs will encourage the further development and application of such acid modification techniques in the future. In addition, the development of new technology, such as two-step alkylation, may be accelerated based on the incentive to reduce catalyst consumption and increase product octane (28).

Improved feedstock pretreatment is important to minimize catalyst consumption and reduce subsequent spent-catalyst handling requirements. Selective hydrogenation of dienes can be used to reduce acid consumption, both in HF and H₂SO₄ alkylation (29). More effective adsorptive treating systems have been applied to remove oxygen-containing contaminants that are frequently introduced in upstream processing steps.

Because solid acid catalyst systems offer advantages with respect to their handling and noncorrosive nature, research on the development of a commercially practical solid acid system to replace the liquid acids will continue. A major hurdle for solid systems is the relatively rapid catalyst deactivation caused by fouling of the acid sites by heavy reaction intermediates and by-products.

Alkylation of Aromatic Hydrocarbons

Most of the industrially important alkyl aromatics used for petrochemical intermediates are produced by alkylating benzene [71-43-2] with monoolefins. The most important monoolefins for the production of ethylbenzene, cumene, and detergent alkylate are ethylene, propylene, and olefins with 10–18 carbons, respectively. This section focuses primarily on these alkylation technologies.

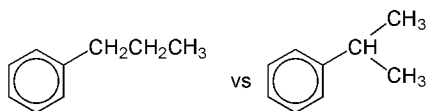
ACID CATALYSTS AND REACTION MECHANISM

Acid catalysts promote the addition of alkyl groups to aromatic rings. Olefins, alcohols, ethers, halides, and other olefin-producing compounds can be used as alkylating reagents. In addition to traditional protonic acid catalysts (H₂SO₄, HF, phosphoric acid) and Friedel-Crafts type catalysts (AlCl₃, boron fluoride), any solid acid catalyst having a comparable acid strength is effective for aromatic alkylation. Typical solid acid catalysts are amorphous and crystalline alumino-silicates, clays, ion-exchange resins, mixed oxides, and supported acids (30). Among these solid acid catalysts, ZSM-5 and Y-type zeolites have become the new commercial catalysts for aromatic alkylation. A new catalytic function, shape selectivity, was found in the application of zeolite catalysts as represented by selective formation of *p*-xylene in toluene alkylation with methanol over a ZSM-5 catalyst (31). The specific catalysts used in the commercial alkylation processes are described in discussions of specific products, eg, for ethylbenzene production.

The first step in the catalytic alkylation of aromatics is the conversion of an olefin or olefin-producing reagent into a carbonium ion or polarized complex. Then, this carbonium ion or complex, which is a powerful electrophile, attacks the aromatic ring (32).

A tertiary carbonium ion is more stable than a secondary carbonium ion, which is in turn more stable than a primary carbonium ion. Therefore, the alkylation of benzene with isobutylene is much easier than is alkylation with ethylene. The reactivity of substituted aromatics for electrophilic substitution is affected by the inductive and resonance effects of a substituent. An electron-donating group, such as the hydroxyl and methyl groups, activates the alkylation; and an electron-withdrawing group, such as chloride, deactivates it.

The rearrangement of carbonium ions that readily occurs according to the thermodynamic stability of cations sometimes limits synthetic utility of aromatic alkylation. For instance, the alkylation of benzene with *n*-propyl bromide gives mostly isopropylbenzene (cumene) C₉H₁₂ and much less *n*-propylbenzene. However, the selectivity to *n*-propylbenzene [103-65-1] versus isopropylbenzene [98-82-8] changes depending on alkylating reagents, conditions, and catalysts;



eg, the alkylation of benzene with *n*-propyl chloride at room temperature gives mostly *n*-propylbenzene (33).

BASE CATALYSTS AND REACTION MECHANISM

Alkali metals and their derivatives can catalyze the alkylation of aromatics with olefins (34). In contrast to acid-catalyzed alkylation, in which the aromatic ring is alkylated, an olefin is added to the alkyl group of aromatics over a base catalyst through a carbanion intermediate. The carbanion intermediate is produced from an aromatic compound by the abstraction of benzylic hydrogen as a proton by a base. The carbanion reacts with an olefin to grow the side chain of the aromatic compound (35).

The side-chain alkylation of toluene with methanol to produce a mixture of styrene and ethylbenzene can be catalyzed by alkali-cation-exchanged X- and Y-type zeolites (36), magnesium oxide [1309-48-4] (MgO), titanium oxide [13463-67-7] (TiO₂), and mixtures of MgO and TiO₂ and calcium oxide [1305-78-8] (CaO) and TiO₂ (37). Toluene is activated on a basic site and reacts with formaldehyde, which is produced from methanol. The coexistence of weak acid sites promotes the reaction (38). The conversion of relatively low cost toluene into more valuable ethylbenzene and styrene is attractive. However, the ethylbenzene or styrene process based on side-chain alkylation has not been developed for commercial applications.

INDUSTRIAL APPLICATION

Ethylbenzene. This alkylbenzene is almost exclusively used as an intermediate for the manufacture of styrene monomer [100-42-5]. A small amount (<1%) is used as a solvent and as an intermediate in dye manufacture (1,39,40). The current ethylbenzene growth rate projections for 1990–1995 range from 3.0 to 3.5% yr (39).

Ethylbenzene [100-41-4] is primarily produced by the alkylation of benzene with ethylene [74-85-1], although a small percentage of the world's ethylbenzene capacity is based on the superfractionation of ethylbenzene from mixed xylenes streams (41). A wide variety of different alkylation processes have been developed and commercialized since the 1940s. These processes can generally be divided into liquid-phase processes and vapor-phase processes.

Liquid-Phase Processes. Prior to 1980, commercial liquid-phase processes were based primarily on an AlCl₃ catalyst. AlCl₃ systems have been developed since the 1930s by a number of companies, including Dow, BASF, Shell Chemical, Monsanto, Soci  t   Chimique des Charbonnages, and Union Carbide–Badger. These processes generally involve ethyl chloride or occasionally hydrogen chloride as a catalyst promoter. Recycled alkylated benzenes are combined with the AlCl₃ and ethyl chloride to form a separate catalyst–complex phase that is heavier than the hydrocarbon phase and can be separated and recycled.

In 1974, Monsanto brought on-stream an improved liquid-phase AlCl₃ alkylation process that significantly reduced the AlCl₃ catalyst used by operating the reactor at a higher temperature (42–44). In this process, the separate heavy catalyst–complex phase previously mentioned was eliminated. Eliminating the catalyst–complex phase increases selectivities and overall yields in addition to lessening the problem of waste catalyst disposal. The ethylbenzene yields exceed 98%.

In the 1980s, environmental pressures associated with the problem of disposal of the waste AlCl₃ catalyst led to the development of two new liquid-phase processes based on zeolite catalysts, which are considered environmentally inert. The first of these processes is a conventional fixed-bed catalyst system (Fig. 3). The catalyst was developed by Unocal, and the process is jointly licensed by Lummus Crest and UOP. The operating conditions with regard to temperature and pressure are mild, and carbon steel can be used throughout the process. The technology has no corrosive elements, and the ethylbenzene yields exceed 98% (45–47). The first commercial unit successfully started in Japan in August, 1990.

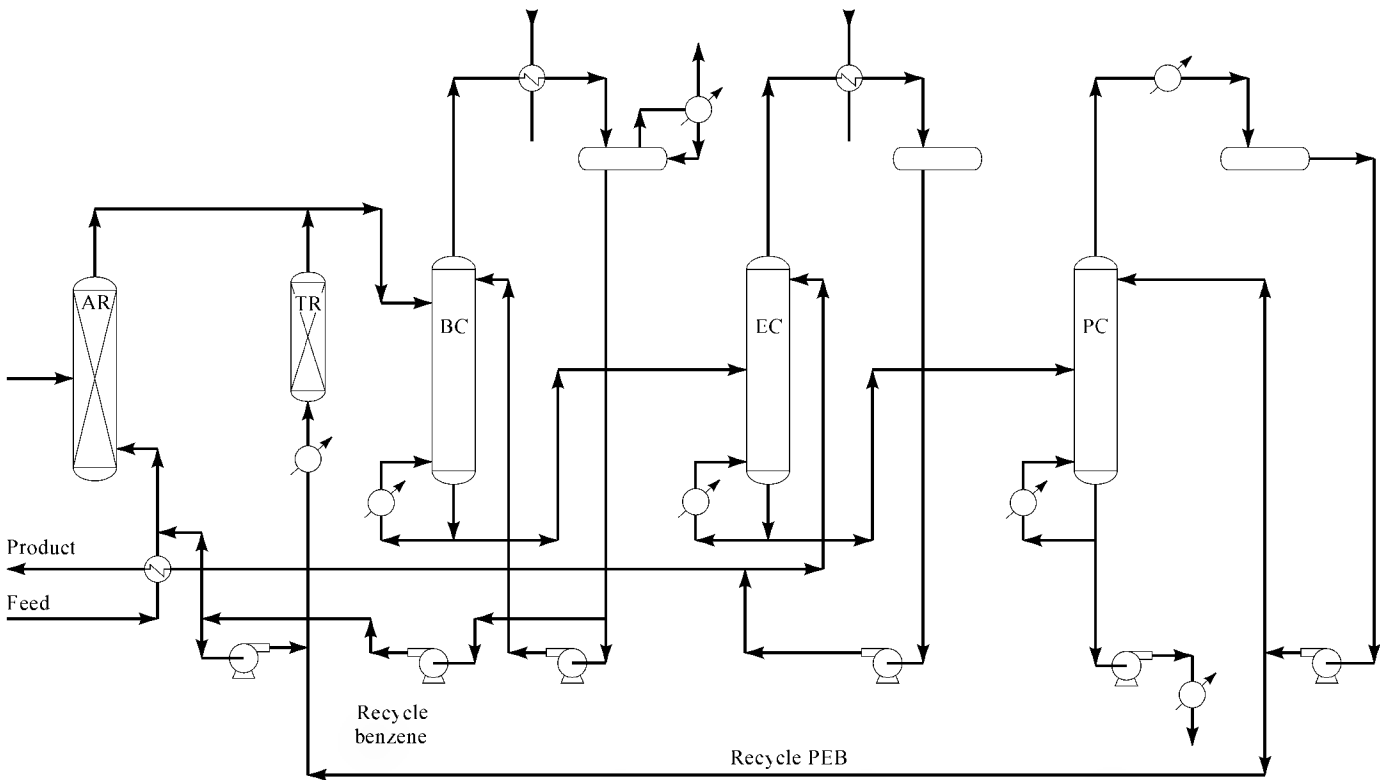


Fig. 3. Unocal–Lummus–UOP ethylbenzene process: AR – alkylation reactor; TR – transalkylation reactor; BC – benzene column; EC – ethylbenzene column; PC – poly(ethylbenzene) (PEB) column.

The second new zeolite-based liquid-phase process was developed by Chemical Research & Licensing Company (CR&L). The process is based on the concept of catalytic distillation, ie, reaction and separation in the same vessel. The concept has been applied commercially for the production of MTBE (48–51) but has not yet been applied commercially for the production of ethylbenzene.

Vapor-Phase Processes. Although vapor-phase alkylation has been practiced since the early 1940s, it could not compete with liquid-phase processes until the 1970s when the Mobil–Badger vapor-phase ethylbenzene process was introduced (Fig. 4). The process is based on Mobil's ZSM-5 zeolite catalyst (38,52,53). The nonpolluting and noncorrosive nature of the process is one of its major advantages over the AlCl_3 liquid-phase system. Unlike the liquid-phase system, the reactors operate at high temperature (400–450°C) and low pressure (2–3 MPa). The high temperature allows the net process heat input and exothermic heat of reaction to be recovered as steam. However, the high temperature vapor-phase operation causes catalytic deactivation by fouling as a result of the deposition of carbonaceous materials, and so the catalyst requires periodic regeneration. Two reactors are required so that processing and regeneration can proceed alternately without interrupting production. Ethylbenzene yields are about 98%.

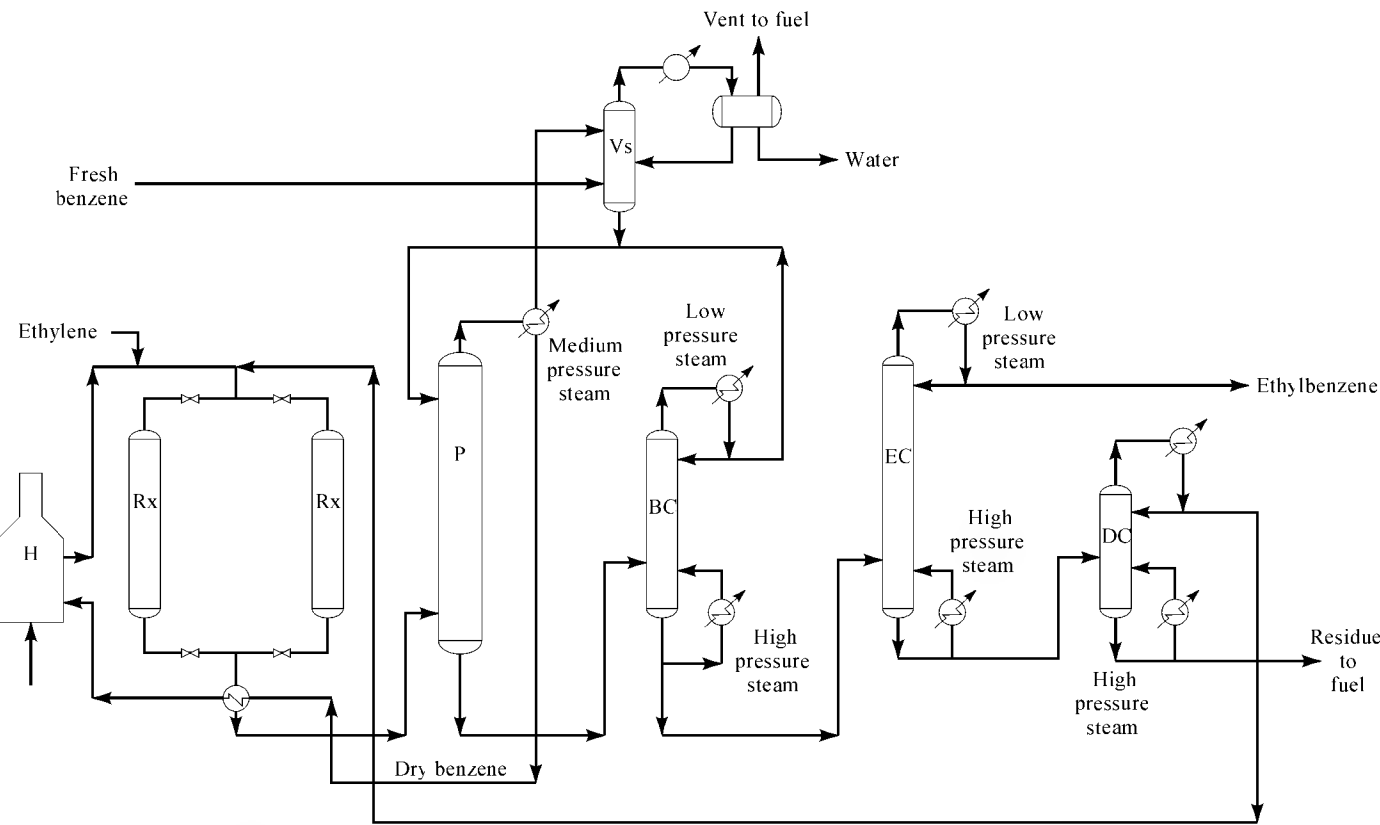


Fig. 4. Mobil–Badger process for ethylbenzene production: H – heater; Rx – reactor; P – prefractionator; BC – benzene recovery column; VS – vent gas scrubber; EC – ethylbenzene recovery column; DC – diethylbenzene recovery column.

Courtesy of VCH Publishers, Inc.

A modified ZSM-5 catalyst has a unique shape-selective property for producing *p*-ethyltoluene [622-96-8] selectively by the alkylation of toluene [108-88-3] with ethylene (54). *p*-Ethyltoluene is an intermediate in the production of poly(*p*-methylstyrene) [24936-41-2] (PPMS), which is reported to have

physical advantages, such as higher flash point and glass-transition temperatures and lower specific gravity, over polystyrene (55,56).

Cumene. Cumene processes were originally developed between 1939 and 1945 to meet the demand for high octane aviation gasoline during World War II (1,2). In 1989, about 95% of cumene demand was as an intermediate for the production of phenol [108-95-2] and acetone [67-64-1]. A small percentage is used for the production of α -methylstyrene. The demand for cumene [98-82-8] has risen at an average rate of 2–3% yr since 1970 (57,58), and this trend is expected to continue throughout the 1990s.

Currently, almost all cumene is produced commercially by two processes: (1) a fixed-bed, kieselguhr-supported phosphoric acid catalyst system developed by UOP and (2) a homogeneous $AlCl_3$ and hydrogen chloride catalyst system developed by Monsanto.

Two new processes using zeolite-based catalyst systems were developed in the late 1980s. Unocal's technology is based on a conventional fixed-bed system. CR&L has developed a catalytic distillation system based on an extension of the CR&L MTBE technology (48–51).

SPA Catalyst. The solid phosphoric acid (SPA) catalyst process has been the dominant source of cumene since the 1930s. This process accounts for more than 90% of cumene operating capacity (59). A simplified process flow diagram is given in Figure 5.

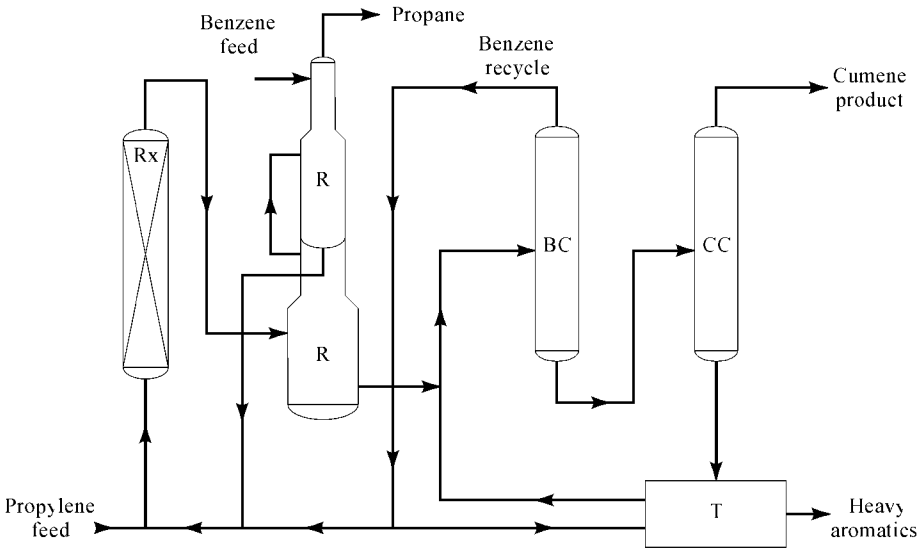


Fig. 5. UOP cumene process: Rx — reactor; R — rectifier; BC — benzene column; CC — cumene column; T = transalkylation.

Propylene feed, fresh benzene feed, and recycle benzene are charged to the upflow reactor, which operates at 3–4 MPa (400–600 psig) and at 200–260°C. The SPA catalyst provides an essentially complete conversion of propylene [115-07-1] on a one-pass basis. A typical reactor effluent yield contains 94.8 wt % cumene and 3.1 wt % diisopropylbenzene [25321-09-9] (DIPB). The remaining 2.1% is primarily heavy aromatics. This high yield of cumene is achieved without transalkylation of DIPB and is unique to the SPA catalyst process.

The cumene product is 99.9 wt % pure, and the heavy aromatics, which have a research octane number (RON) of 109, can either be used as high octane gasoline-blending components or combined with additional benzene and sent to a transalkylation section of the plant where DIPB is converted to cumene. The overall yields of cumene for this process are typically 97–98 wt % with transalkylation and 94–96 wt % without transalkylation.

$AlCl_3$ and Hydrogen Chloride Catalyst. Historically, $AlCl_3$ processes have been used more extensively for the production of ethylbenzene than for the production of cumene. In 1976, Monsanto developed an improved cumene process that uses an $AlCl_3$ catalyst, and by the mid-1980s, the technology had been successfully commercialized. The overall yields of cumene for this process can be as high as 99 wt % based on benzene and 98 wt % based on propylene (60).

A simplified process flow diagram is shown in Figure 6 (61). Dry benzene, fresh and recycle, and propylene are mixed in the alkylation reaction zone with the $AlCl_3$ and hydrogen chloride catalyst at a temperature of less than 135°C and a pressure of less than 0.4 MPa (50 psig) (61). The effluent from the alkylation zone is combined with recycle polyisopropylbenzene and fed to the transalkylation zone, where polyisopropylbenzenes are transalkylated to cumene. The strongly acidic catalyst is separated from the organic phase by washing the reactor effluent with water and caustic.

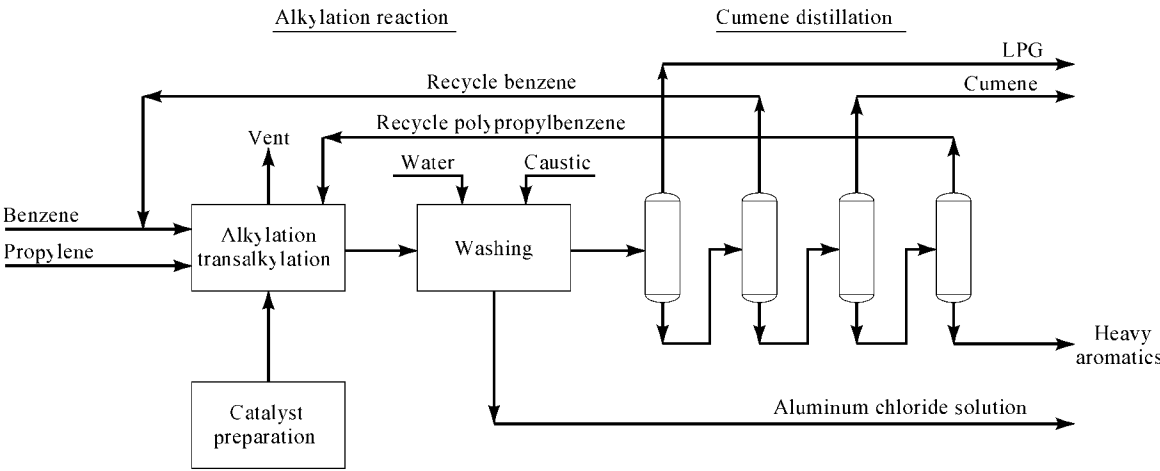


Fig. 6. Monsanto-Lummus Crest cumene process.

The distillation system is designed to recover a high purity cumene product. The unconverted benzene and polyisopropylbenzenes are separated and recycled to the reaction system. Propane in the propylene feed is recovered as liquid petroleum gas (LPG).

Zeolite Catalysts. Unocal has introduced a fixed-bed liquid-phase reactor system based on a Y-type zeolite catalyst (62). The selectivity to cumene is generally between 70 and 90 wt %. The remaining components are primarily polyisopropylbenzenes, which are transalkylated to cumene in a separate reaction zone to give an overall yield of cumene of about 99 wt %. The distillation requirements involve the separation of propane for LPG use, the recycle of excess benzene to the reaction zones, the separation of polyisopropylbenzene for transalkylation to cumene, and the production of a purified cumene product.

The second zeolite process, which was developed by CR&L, is based on the concept of catalytic distillation (48–51), which is a combination of

catalytic reaction and distillation in a single column. The basic principle is to use the heat of reaction directly to supply heat for fractionation. This concept has been applied commercially for the production of MTBE but has not yet been applied commercially to cumene.

Cymene. Methylisopropylbenzene [25155-15-1] can be produced over a number of different acid catalysts by alkylation of toluene with propylene (63–66). Although the demand for cymene is much lower than for cumene, one commercial plant was started up in 1987 at the Yan Shan Petrochemical Company in the People's Republic of China. The operation of this plant is based on SPA technology offered by UOP for cumene. The cymene is an intermediate for the production of *m*-cresol (3-methylphenol) [108-39-4].

Detergent Alkylate. In the 1940s, sodium dodecylbenzene sulfonate [25155-30-0] (DDBS) produced by the alkylation of benzene with propylene tetramer (C₁₂H₂₄) followed by sulfonation with oleum [8014-95-7] (H₂SO₄ mixture with sulfur trioxide) or sulfur trioxide and then neutralization was found to have detergent characteristics superior to those of natural soaps. Because of its price stability and effectiveness, DDBS became the standard synthetic surfactant in the industry. By 1955, these efficient surfactants were also leading to environmental problems, such as buildup of foam in downstream discharge sites. This buildup was attributed to the poor biodegradability of the highly branched structure of the propylene tetramer [6842-15-5] (67–69).

During the early 1960s, linear aliphatic olefins, such as α olefins produced via ethylene oligomerization or linear internal olefins produced via catalytic dehydrogenation of linear paraffins, replaced the use of propylene tetramers in industrialized countries, and production of more biodegradable linear alkylbenzene sulfonates (LABS) began (see [ADSORPTION, LIQUID SEPARATION](#)) (70). Except in a few parts of the world, the use of DDBS was phased out by 1980.

The synthetic detergent industry has become one of the largest chemical process industries (see DETERGENCY). Sales in 1989 were estimated at more than \$4 billion in the United States alone. As of 1989, the worldwide annual production of linear alkylbenzene (LAB) and branched alkylbenzene (DDB) was estimated to be about 1.8 million tons and 230,000 tons, respectively (71,72).

Industrial Processes. Two catalysts, HF and AlCl_3 , are widely used for the alkylation of benzene with higher olefins (C_{10} – C_{15} , detergent-range olefins). In some earlier units, H_2SO_4 was used. In addition to the alkylation activity, all of these acid catalysts possess, in varying degrees, activity to shift the olefinic double bond along the chain. Thus, regardless of the position of the double bond in the olefin feed, the position of the phenyl group in the final product, as shown in Table 2 for the reaction of 1-dodecene [112-41-4] with benzene, is specific to the catalyst system used (73,74). Regardless of the catalyst system used, minor side reactions, like the formation of dialkylbenzene, take place.

Table 2. Isomer Distribution, wt %, of Dodecylbenzene from 1-Dodecene and Benzene

Phenyl position		Catalyst system		
		HF	AlCl ₃	H ₂ SO ₄
1	0	0	0	
2	20	32	41	
3	17	22	20	
4	16	16	13	
5	23	15	13	
6	24	15	13	

AlCl₃ Alkylation Process. The first step in the AlCl₃ process is the chlorination of *n*-paraffins to form primary monochloroparaffin. Then in the second step, the monochloroparaffin is alkylated with benzene in the presence of AlCl₃ catalyst (75,76). Considerable amounts of indane [2,3-dihydro-1*H*-indene [496-11-7)] and tetralin (1,2,3,4-tetrahydronaphthalene [119-64-2]) derivatives are formed as by-products because of the dichlorination of paraffins in the first step (77). Only a few industrial plants built during the early 1960s use this technology to produce LAB from linear paraffins. The C₁₀–C₁₅ α olefins also can be alkylated with benzene using this catalyst system.

HF Alkylation Process. The most widely used technology today is based on the HF catalyst system. All industrial units built in the free world since 1970 employ this process (78). During the mid-1960s, commercial processes were developed to selectively dehydrogenate linear paraffins to linear internal olefins (79–81). Although these linear internal olefins are of lower purity than are α olefins, they are more cost-effective because they cost less to produce. Furthermore, with improvement over the years in dehydrogenation catalysts and processes, such as selective hydrogenation of diolefins to monoolefins (82,83), the quality of linear internal olefins has improved.

A simplified flow diagram for a typical UOP linear detergent alkylation unit is shown in Figure 7. The design of this unit is similar to a unit that produces branched-chain detergent alkylate.

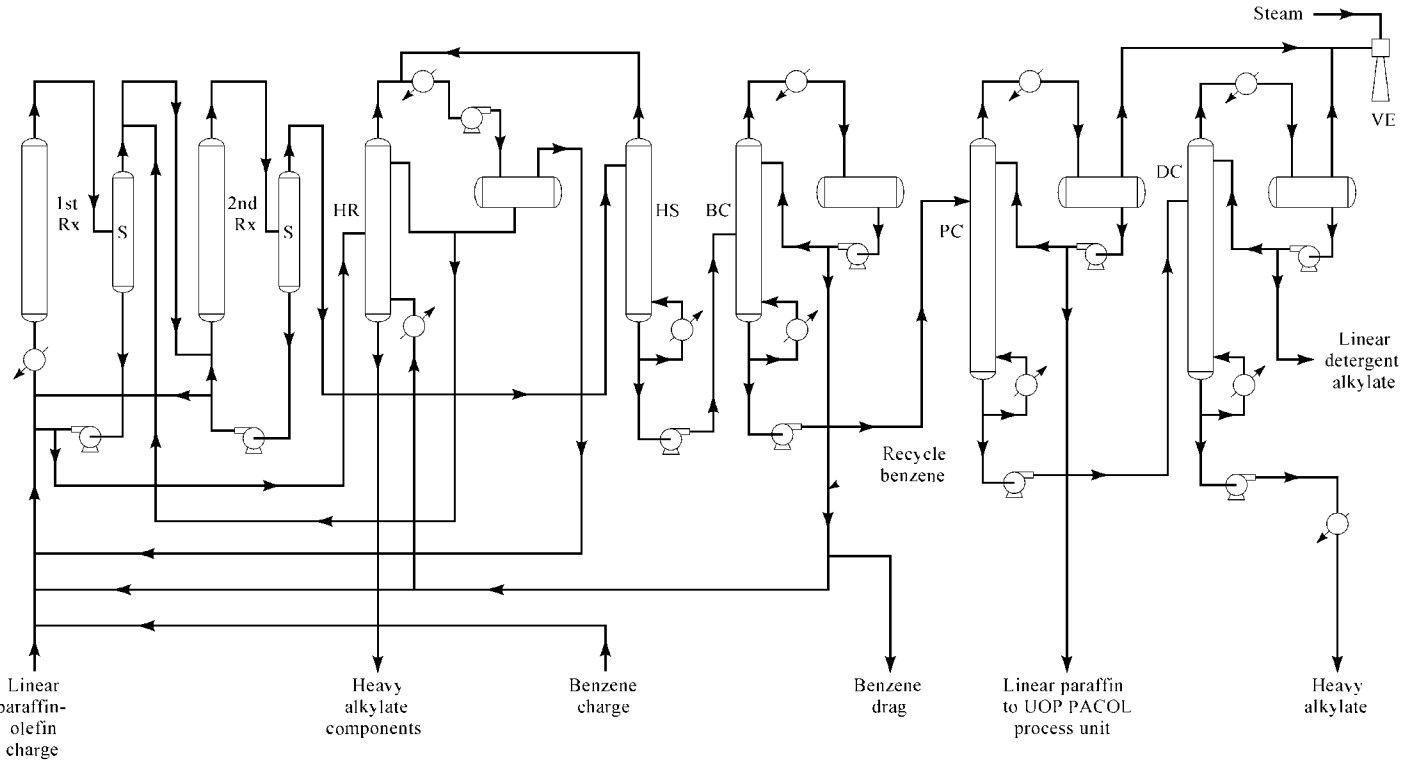
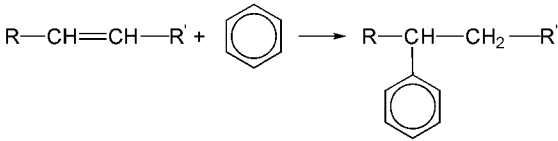


Fig. 7. UOP linear detergent alkylate process: Rx reactor; S settler; HR HF regenerator; HS HF stripper; BC benzene column;

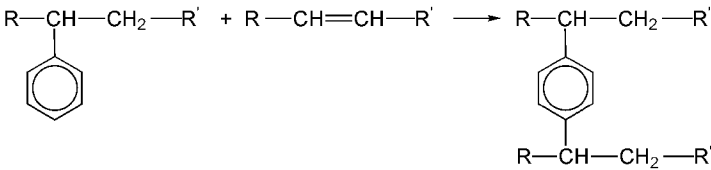
PC paraffin column; DC detergent alkylate column; VE vacuum ejector.

A necessary feature of the alkylation reaction section is the use of two reactors: the first-stage reactor completes the major part of the alkylation reaction, and in the second-stage reactor the last traces of unsaturated hydrocarbons react, and a sizable portion of the soluble polyaromatics is removed. Modern units with lower-diene-containing feeds employ a single alkylation reactor (79).

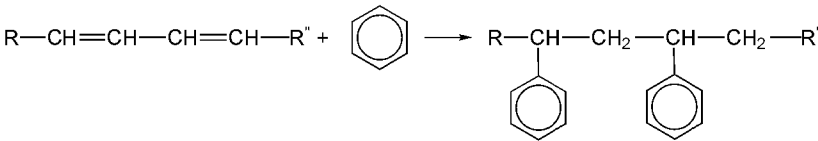
The following HF alkylation reactions are based on straight-chain olefins. A similar chemistry can be written for the branched-chain process. The main reaction is the alkylation of benzene with the straight-chain olefins to yield a linear alkylbenzene:



At the existing conditions, some side reactions, such as the formation of dialkylbenzene, take place:



The diolefins react to form diphenylalkanes:



Some heavier compounds are formed by a combination of these reactions.

High purity olefin feed or an olefin–paraffin mixture from a dehydrogenation unit is combined with makeup and recycle benzene and cooled prior to mixing with HF acid. The reaction section consists of a mixer reactor and an acid settler. Because of dilution by excess benzene and paraffin, the temperature rise resulting from the exothermic reaction is relatively small. A portion of the HF phase from the settler is sent to the HF regenerator, where heavy by-products are removed to maintain the required purity of the HF acid. The hydrocarbon phase from the acid settler proceeds to the fractionation section, where the remaining HF catalyst, excess benzene, unreacted *n*-paraffins, heavy alkylate, and the LAB product are separated by means of sequential fractionation columns. The HF acid and benzene are recycled to the alkylation reactor. The unreacted *n*-paraffins are passed through an alumina treater to remove combined fluorides and are then recycled back to the dehydrogenation unit. Not shown in Figure 7 is the HF acid handling and neutralization section. This section is not basic in the process but is required for the safe operation of the unit (84).

Future Developments. The most recent advance in detergent alkylation is the development of a solid catalyst system. UOP and Compania Espanola de Petroleos SA (CEPSA) have disclosed the joint development of a fixed-bed heterogeneous aromatic alkylation catalyst system for the production of LAB. Petresa, a subsidiary of CEPSA, has announced plans for the construction of a 75,000 t yr LAB plant in Quebec, Canada, that will use the UOP *n*-paraffin dehydrogenation process and the new fixed-bed alkylation process (85).

Some details of this new process have been published by UOP (86). UOP claims equal or better LAB product quality via the fixed-bed process compared with the conventional liquid-phase process employing HF acid catalyst. The new technology requires approximately 15% lower capital investment, mostly the result of the elimination of safety equipment and equipment related to HF acid neutralization.

Table 3 shows typical properties of linear detergent alkylates produced via AlCl₃, HF, and new UOP Detal catalyst systems (86,87).

Table 3. Typical LAB Product Properties

Property	AlCl ₃ alkylate	HF alkylate	Detal alkylate
specific gravity	0.860	0.860	0.860
bromine number	0.015	0.015	0.015
Saybolt color	±30	±30	±30
Doctor test	negative	negative	negative
water, wt %	0.01	0.01	0.01
sulfonation, wt %	98.5	98.5	98.5
biodegradability, wt %	95	95	95
paraffins, wt %	0.3	0.3	0.3
indanes or tetralins, wt %	5–15	1–3	1–3
2-phenylalkanes, wt %	30	15	25
<i>n</i> -alkylbenzene, wt %	90	94	94
average molecular weight	235–260	235–260	235–260

Xylenes. The main application of xylene isomers, primarily *p*- and *o*-xylenes, is in the manufacture of plasticizers and polyester fibers and resins. Demands for xylene isomers and other aromatics such as benzene have steadily been increasing over the last two decades. The major source of xylenes is the catalytic reforming of naphtha and the pyrolysis of naphtha and gas oils. A significant amount of toluene and C₉₊ aromatics, which have lower petrochemical value, is also produced by these processes. More valuable *p*- or *o*-xylene isomers can be manufactured from these low value aromatics in a process complex consisting of transalkylation, eg, the Tatoray process and Mobil's toluene disproportionation (MTDP) and selective toluene disproportionation (MSTDP) processes; isomerization, eg, the UOP Isomar process (88) and Mobil's high temperature isomerization (MHTI), low pressure isomerization (MLPI), and vapor-phase isomerization (MVPI) processes (89); and xylene isomer separation, eg, the UOP Parex process (90).

The Tatoray process, which was developed by Toray Industries, Inc., and is available for license through UOP, can be applied to the production of xylenes and benzene from feedstock that consists typically of toluene [108-88-3], either alone or blended with C₉ aromatics (particularly trimethylbenzenes and ethyl-toluenes). The main reactions are transalkylation (or disproportionation) of toluene to xylene and benzene or of toluene and trimethylbenzenes to xylenes in the vapor phase over a highly selective fixed-bed catalyst in a hydrogen atmosphere at 350–500°C and 1–5 MPa (10–50 atm). Ethyl groups are

dealkylated or converted into methyl groups at high temperature conditions (91,92).

The MTDP process, which is similar to the Tatoray process, produces an equilibrium composition of xylene isomers. A *p*-xylene yield of 24% in the xylene product is formed at 42–48 wt % toluene conversion over the heterogeneous catalyst at 390–495°C, 4.2 MPa (600 psig), 1–2 h⁻¹ liquid hourly space velocity, and 4 H₂ hydrocarbon molar feed ratio. A new ZSM-5 catalyst, which has higher activity and stability than the current catalyst, has been reported (93).

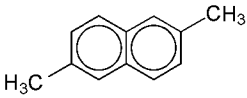
The MSTDP process produces *p*-xylene [106-42-3] (*p*-dimethylbenzene) over a pretreated modified ZSM-5 catalyst at concentrations in the xylene products that range from 80 to 93% depending on catalyst pretreatment and operating conditions. A *p*-xylene concentration higher than an equilibrium concentration of 24% results from the much greater diffusivity of *p*-xylene in the ZSM-5 pore structure than that of ortho and meta isomers and the selective deactivation of active sites on the exterior surface of the ZSM-5 crystals by the pretreatment. Toluene conversions of 25–32 wt % are achieved at 2–6 h⁻¹ weight hourly space velocity, 400–420°C, 2.3–3.5 MPa (300–500 psig), and 1–4 H₂ hydrocarbon molar feed ratio. This process was commercialized by the Enichem Petrochemical Plant in Gela, Italy (94).

The Xylene Plus process of ARCO Technology, Inc. (95,96) and the FINA T2BX process (97) also use a fixed-bed catalyst in the vapor phase for transalkylation of toluene to produce xylenes and benzene. The Mobil low temperature disproportionation (LTD) process employs a zeolite catalyst for transalkylation of toluene in the liquid phase at 260–315°C in the absence of hydrogen (98).

The selective alkylation of toluene with methanol to produce *p*-xylene as a predominant isomer can be achieved over shape-selective catalysts (99–101). With a modified ZSM-5 zeolite catalyst, more than 99% *p*-xylene in xylene isomers can be produced at 550°C. This *p*-xylene concentration exceeds the equilibrium concentration of 23% (99). The selective synthesis of *p*-xylene using relatively low cost toluene is economically attractive; however, this technology was not commercialized as of 1991.

Polynuclear Aromatics. The alkylation of polynuclear aromatics with olefins and olefin-producing reagents is effected by acid catalysts. The alkylated products are more complicated than are those produced by the alkylation of benzene because polynuclear aromatics have more than one position for substitution. For instance, the alkylation of naphthalene [91-20-3] with methanol over mordenite and Y-type zeolites at 400–450°C produces 1-methylnaphthalene [90-12-0] and 2-methylnaphthalene at a 2- 1- ratio of about 1.8. The selectivity to 2-methylnaphthalene [91-57-6] is increased by applying a ZSM-5 catalyst to give a 2- 1- ratio of about 8 (102).

2,6-Dimethylnaphthalene [581-42-0] (2,6-DMN) can be a precursor for 2,6-naphthalenedicarboxylic acid [1141-38-4], which is a starting material for high performance polyesters or polyamides.



2,6-DMN can be produced by alkylating naphthalene or 2-methylnaphthalene at 250–450°C over zeolite catalysts (102,103). However, no commercial technology by this synthetic route had been developed as of 1991, primarily because of low catalytic selectivity.

FUTURE TECHNOLOGY TRENDS

Over the years, improvements in aromatic alkylation technology have come in the form of both improved catalysts and improved processes. This trend is expected to continue into the future.

Catalysts. Nearly all of the industrially significant aromatic alkylation processes of the past have been carried out in the liquid phase with unsupported acid catalysts. For example, AlCl₃ and HF have been used commercially for at least one of the benzene alkylation processes to produce ethylbenzene (104), cumene (105), and detergent alkylates (80). Exceptions to this historical trend have been the use of a supported boron trifluoride for the production of ethylbenzene and of a solid phosphoric acid (SPA) catalyst for the production of cumene (59,106).

Since 1976, these forms of acids have become a significant environmental concern from both a physical handling and disposal perspective. This concern has fueled much development work toward solid acid catalysts, including zeolites, silica –aluminas, and clays (107,108).

Two catalysts have emerged as commercially viable. The Mobil–Badger ethylbenzene process, which has been in commercial use since 1980, employs a zeolite catalyst and operates in the gas phase. A liquid-phase ethylbenzene process jointly licensed by Lummus and UOP uses a Y-type zeolite catalyst developed by Unocal. This liquid-phase process was commercialized in 1990. The same Y-type zeolite catalyst used for the production of ethylbenzene is being offered for the production of cumene but has not yet been commercialized.

Because of their initial commercial success and the industry’s growing awareness of environmental issues, solid acid catalysts are expected to ultimately replace liquid acid catalysts. Several publications describe the use of solid acid catalysts for the production of cumene and detergent alkylates (62,85–87,109).

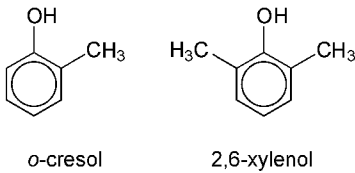
Process. As solid acid catalysts have replaced liquid acid catalysts, they have typically been placed in conventional fixed-bed reactors. An extension of fixed-bed reactor technology is the concept of catalytic distillation being offered by CR&L (48). In catalytic distillation, the catalytic reaction and separation of products occur in the same vessel. The concept has been applied commercially for the production of MTBE and is also being offered for the production of ethylbenzene and cumene.

A new alkylation process called Alkymax was introduced by UOP in 1990. This process was developed in response to proposed legislation requiring the reduction of benzene (a known carcinogen) in gasoline (110). Refinery propylene, typically from a fluid catalytic cracker, is used to alkylate the benzene in light reformate (111). In addition to lowering the benzene content, the alkylate formed has a high octane value and can typically boost the octane of the gasoline pool by 0.5 RON.

Other Alkylations

Alkylation of Phenol. The hydroxyl group activates the alkylation of the benzene ring because it is a strong electron-donating group; therefore, the alkylation of phenol [108-95-2] can be achieved with olefins and olefin-producing reagents under milder conditions than the alkylation of aromatic hydrocarbons. The alkylation of phenol with olefins and other alkylating reagents is discussed in references 112 and 113 (see also ALKYLPHENOLS).

Alkylated phenol derivatives are used as raw materials for the production of resins, novolaks (alcohol-soluble resins of the phenol–formaldehyde type), herbicides, insecticides, antioxidants, and other chemicals. The synthesis of 2,6-xylenol [576-26-1] has become commercially important since PPO resin, poly(2,6-dimethyl phenylene oxide), an engineering thermoplastic, was developed (114,115). The demand for *o*-cresol and 2,6-xylenol (2,6-dimethylphenol) increased further in the 1980s along with the growing use of epoxy cresol novolak (ECN) in the electronics industries and poly(phenylene ether) resin in the automobile industries. The ECN is derived from *o*-cresol, and poly(phenylene ether) resin is derived from 2,6-xylenol.

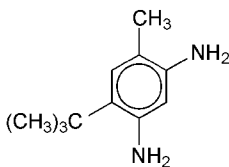


Cresol and xylenol can be prepared by the methylation of phenol with methanol over both acid and base catalysts. It is postulated that phenol methylation on acid catalysts proceeds through the initial formation of anisole (methoxybenzene [100-66-3]) followed by intramolecular rearrangement of

the methyl group to form *o*-cresol. The methyl group in the ortho position can further undergo isomerization to form meta and para isomers. The formation of *m*- and *p*-cresols is accelerated at higher temperatures and with stronger acid catalysts (116,117). Xylenol isomers are produced by the consecutive methylation of cresol isomers. The methylation of phenol is more selective to *o*-cresol with base catalysts than with acid catalysts. On base catalysts, phenol adsorbs dissociatively on a pair of basic and acidic sites to form a protonic site and an adsorbed phenolate species, respectively. This proton site activates methanol to produce a carbonium ion, which reacts with the benzene ring of an adjacently adsorbed phenolate species at the ortho position (113).

The commercial process for the selective synthesis of *o*-cresol [95-48-7] and 2,6-xylenol by the alkylation of phenol with methanol in a fixed-bed reactor was developed by the General Electric Company. The high selectivity is effected by using a magnesium oxide catalyst at high temperatures (475–600°C). The alkylation occurs at the positions ortho to the hydroxyl group. Because the catalyst does not have isomerization activity, the products are *o*-cresol, 2,6-xylenol, and minor amounts of 2,4,6-trimethylphenol [527-60-6] and anisole [100-66-3] (118). Similar commercial processes using a fixed-bed reactor system have been commercialized by BASF, Groda, and Mitsubishi Gas Chemicals (119). A new phenol methylation process technology for the production of *o*-cresol and 2,6-xylenol has recently been developed by Asahi Chemical Industry (119,120). This new process uses a new catalyst and a fluidized-bed reactor. The catalyst is a silica-supported iron–vanadium mixed oxide modified by metal promoters. This catalyst is active at 300–350°C and is selective for *o*-cresol and 2,6-xylenol formation. The catalyst-bed temperature can be maintained uniformly at relatively low temperatures because of the high heat-transfer efficiency of the fluidized-bed reactor system; therefore, side reactions caused at high temperatures are eliminated and the catalyst life becomes long. Because no significant amount of meta and para isomers is produced in this process, high purity *o*-cresol (99.95%) and 2,6-xylenol (99.85%) can be produced.

Alkylation of Aromatic Amines and Pyridines. Commercially important aromatic amines are aniline [62-53-3], toluidine [26915-12-8], phenylenediamines [25265-76-3], and toluenediamines [25376-45-8] (see AMINES, AROMATIC). The ortho alkylation of these aromatic amines with olefins, alcohols, and dienes to produce more valuable derivatives can be achieved with solid acid catalysts. For instance, 5-*tert*-butyl-2,4-toluenediamine (C₁₁H₁₈N₂), which is used for performance polymer applications, is produced at 85% selectivity and 84% 2,4-toluenediamine [95-80-7] (2,4-TDA) conversion by alkylation of 2,4-TDA with isobutylene over a Y-type zeolite catalyst at 180–200°C (121).



The alkylation of pyridine [110-86-1] takes place through nucleophilic or homolytic substitution because the π -electron-deficient pyridine nucleus does not allow electrophilic substitution, eg, Friedel-Crafts alkylation. Nucleophilic substitution, which occurs with alkali or alkaline metal compounds, and free-radical processes are not attractive for commercial applications. Commercially, catalytic alkylation processes via homolytic substitution of pyridine rings are important. The catalysts effective for this reaction include boron phosphate, alumina, silica–alumina, and Raney nickel (122).

Health and Safety Factors

Generally, specific health and safety factors relating to feedstock and products must be addressed for each particular industrial alkylation process. The reader is referred to the sections of the encyclopedia that describe specific chemical compounds. In addition, the properties of the catalyst systems employed in alkylation must be considered. The hazardous properties of the homogeneous acid catalysts, HF, H₂SO₄, and AlCl₃, are documented in other sections of this encyclopedia (see ALUMINUM COMPOUNDS; FLUORINE COMPOUNDS, INORGANIC; SULFURIC ACID AND SULFUR TRIOXIDE). In industrial applications, specialized procedures are required to ensure the safe handling of these materials. Replacing these materials with solid acid catalysts will become more important in the future. The solid acid catalysts themselves present a disposal problem that favors the development of regenerable catalysts or the implementation of recycling procedures.

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ALKYLBENZENES.

See BTX PROCESSING; CUMENE; TOLUENE; XYLENES AND ETHYLBENZENE.

ALKYL HALIDES.

See BROMINE COMPOUNDS; CHLOROCARBONS AND CHLOROHYDROCARBONS; FLUORINE COMPOUNDS, ORGANIC; IODINE AND IODINE COMPOUNDS.

ALKYLPHENOLS

The production of alkylphenols exceeds 450,000 t yr on a worldwide basis. Alkylphenols of greatest commercial importance have alkyl groups ranging in size from one to twelve carbons. The direct use of alkylphenols is limited to a few minor applications such as epoxy-curing catalysts and biocides. The vast majority of alkylphenols are used to synthesize derivatives which have applications ranging from surfactants to pharmaceuticals. The four principal markets are nonionic surfactants, phenolic resins, polymer additives, and agrochemicals.

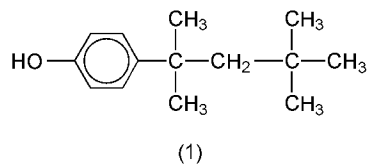
Nonionic surfactants and phenolic resins based on alkylphenols are mature markets and only moderate growth in these derivatives is expected. Concerns over the biodegradability and toxicity of these alkylphenol derivatives to aquatic species may limit their use in the future. The use of alkylphenols in the production of both polymer additives and monomers for engineering plastics is expected to show above average growth as plastics continue to replace traditional building materials.

Alkylphenols containing 3–12-carbon alkyl groups are produced from the corresponding alkenes under acid catalysis. Alkylphenols containing the methyl group were traditionally extracted from coal tar. Today they are produced by the alkylation of phenol with methanol.

Nomenclature

An alkylphenol is a phenol derivative wherein one or more of the ring hydrogens has been replaced by an alkyl group(s). Phenol is a heading parent in the CAS indexing system. Appropriate names of alkylphenols for abstract citations can be derived by using the appropriate aids (1). The names generated in this manner are unambiguous and refer to a specific compound, but are lengthy and cumbersome to use. Common names are used on a daily basis and are especially prevalent for alkylphenols that have gained commercial importance.

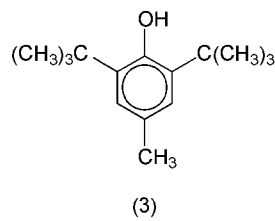
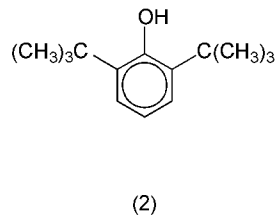
For monosubstituted alkylphenols, the position of the alkyl radical relative to the hydroxyl function is designated either with a numerical locant or ortho, meta, or para. The alkyl side chain typically retains a trivial name. Thus 4-(1,1,3,3-tetramethylbutyl)phenol, 4-*tert*-octylphenol, and *para-tert*-octylphenol (PTOP) all refer to structure (1).

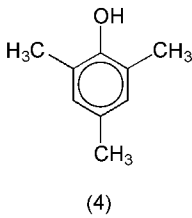


Dialkylphenols employ locants to designate the position of the alkyl groups on the ring. Thus, 2,6-bis(1,1-dimethylethyl)phenol, 2,6-di-*tert*-butylphenol, and 2,6-DTBP each refer to structure (2).

Other common names are cresol and xlenol for methyl- and dimethylphenols respectively, eg, *o*-cresol is 2-methylphenol, and 2,5-xlenol is 2,5-dimethylphenol.

For phenols with three or more alkyl substituents, trade names, abbreviations, and associative names predominate, eg, BHT and 2,6-di-*tert*-butyl-4-methylphenol refer to structure (3) and mesitol and 2,4,6-trimethylphenol refer to structure (4).





Physical Properties

Of course, the physical properties of alkylphenols are comparable to phenol. The properties are strongly influenced by the type of alkyl substituent and its position on the ring. Alkylphenols, like phenol, are typically solids at 25°C. Their form is affected by the size and configuration of the alkyl group, its position on the ring, and purity. They appear colorless, or white, to a pale yellow when pure (Table 1).

Table 1. Commercially Important Alkylphenols

Name	CAS Registry Number	Molecular formula	Molecular weight	Physical form at 25°C	Boiling point, °C ^a	Freezing point, °C	Density ^b , g mL	Typical Assay	Flash point, °C	Molten color APHA
4- <i>tert</i> -amylphenol	[80-46-6]	C ₁₁ H ₁₄ O	164.0	solid	249	90.0	0.915 ¹⁰⁷	99	121	200
4- <i>tert</i> -butylphenol	[98-54-4]	C ₁₀ H ₁₄ O	150.2	solid	237	97.5	0.890 ¹⁰⁷	98–99	117	100
2- <i>sec</i> -butylphenol	[89-72-5]	C ₁₀ H ₁₄ O	150.2	liquid	224	20.0	0.938 ⁴³	98	>93	100
4-cumylphenol	[599-64-4]	C ₁₅ H ₁₄ O	212.0	solid	335	70.0	1.029 ⁹³	99	188	100
4-dodecylphenol	[27193-86-8]	C ₁₈ H ₃₀ O	262.0	liquid	334	<20.0	0.914 ²⁰	89–95	>100	500
4-nonylphenol	[84852-15-3] ^f	C ₁₅ H ₂₄ O	220.3	liquid	310	<20.0	0.933 ⁴³	90–95	146	100
4- <i>tert</i> -octylphenol	[140-66-9]	C ₁₄ H ₂₂ O	220.3	solid	290	81.0	0.940 ²⁵	90–98	132	200
2,4-di- <i>tert</i> -amylphenol	[25231-47-4]	C ₁₄ H ₂₀ O	234.4	liquid	275	23.0	0.900 ⁴⁰	99	104	100
2,4-di- <i>tert</i> -butylphenol	[96-76-4]	C ₁₄ H ₂₂ O	206.3	solid	263	52.0	0.867 ⁸²	99	115	100
2,6-di- <i>tert</i> -butylphenol	[128-39-2]	C ₁₄ H ₂₂ O	206.3	solid	253	36.0	0.898 ⁴³	99	>99	100
di- <i>sec</i> -butylphenol	[31291-60-8]	C ₁₄ H ₂₂ O	206.3	liquid		<20.0	0.902	90	127	500
2,4-dicumylphenol	[2772-45-4]	C ₂₄ H ₂₀ O	330.0	solid		65.0	1.030	99	462	100
2-methylphenol	[95-48-7]	C ₇ H ₈ O	108.1	solid	191	30.0	1.049 ^{15 5}	99	81	25
3-methylphenol	[108-39-4]	C ₇ H ₈ O	108.1	liquid	202	10.0	1.042 ^{15 5}	97	86	
4-methylphenol	[106-44-5]	C ₇ H ₈ O	108.1	solid	202	34.0	1.022 ²⁵	99	86	25
2,6-dimethylphenol	[576-26-1]	C ₈ H ₁₀ O	122.1	solid	203	48.0	1.020 ²⁵	99	88	

^a At 101.3 kPa = 1 atm.
^b At the temperature indicated by the superscript, °C.
^c Mixture, branched chains.

Para-alkylphenols have higher melting points and boiling points than the corresponding ortho-isomers. The melting points of para-alkylphenols go through a maximum for *tert*-butyl and then decrease. An alkene stream consisting of a mixture of isomers produces an alkylphenol that has a depressed melting point. As the carbon chain of the alkyl group surpasses 20, the resulting phenols take on a waxy form. Alkylphenols, especially when di- and trisubstituted, tend to supercool. Alkylphenols show the same sensitivity to oxidation that phenol does. The presence of trace amounts of metals or alkaline impurities accelerates oxidation. Oxidation products cause discoloration.

The solubility of alkylphenols in water falls off precipitously as the number of carbons attached to the ring increases. They are generally soluble in common organic solvents: acetone, alcohols, hydrocarbons, toluene. Solubility in alcohols or heptane follows the generalization that "like dissolves like." The more polar the alkylphenol, the greater its solubility in alcohols, but not in aliphatic hydrocarbons; likewise with cresols and xylenols. The solubility of an alkylphenol in a hydrocarbon solvent increases as the number of carbon atoms in the alkyl chain increases. High purity para substituted phenols, C₃ through C₈, can be obtained by crystallization from heptane.

The aromatic ring of alkylphenols imparts an acidic character to the hydroxyl group; the pK_a of unhindered alkylphenols is 10–11 (2). Alkylphenols unsubstituted in the ortho position dissolve in aqueous caustic. As the carbon number of the alkyl chain increases, the solubility of the alkali phenolate salt in water decreases, but aqueous caustic extractions of alkylphenols from an organic solution can be accomplished at elevated temperatures. Bulky ortho substituents reduce the solubility of the alkali phenolate in water. The term cryptophenol has been used to describe this phenomenon. A 35% solution of potassium hydroxide in methanol (Claisen's alkali) dissolves such hindered phenols (3).

Alkyl groups in the ortho position affect the environment about the hydroxyl group; the larger the group the greater the effect. Intermolecular hydrogen bonding decreases with the introduction of a *tert*-butyl group ortho to the hydroxyl, reducing the atmospheric boiling point of the ortho isomer by about 20°C. Substitution of the second ortho position with a *tert*-butyl group effectively precludes any hydrogen bonding as shown by the infrared spectrum of 2,6-DTBP; a sharp absorbance is found at 2.75 μm, characteristic of an unassociated hydroxyl stretching (4). The impact of an ortho alkyl substituent on hydrogen bonding can be advantageously applied to the analysis and separation of alkylphenols. A mixture of ortho and para isomers is separated effectively using normal phase chromatography (flash or hplc).

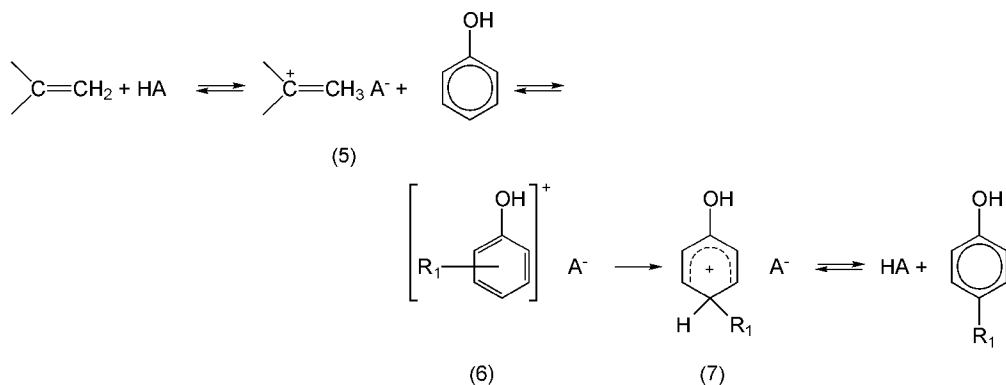
There is a health benefit associated with hindering hydrogen bonding. Alkylphenols as a class are generally regarded as corrosive health hazards, but this corrosivity is eliminated when the hydroxyl group is flanked by bulky substituents in the ortho positions. In fact, hindered phenols as a class of compounds are utilized as antioxidants in plastics with FDA approval for indirect food contact.

Synthesis of Alkylphenols

Alkylphenols can be synthesized by several approaches, including alkylation of a phenol, hydroxylation of an alkylbenzene, dehydrogenation of an alkylcyclohexanol, or ring closure of an appropriately substituted acyclic compound. The choice of approach depends on the target alkylphenol, availability of the starting materials, and cost of processing. The procedures discussed herein encompass commercial methods, general methods, and a few specific examples of commercial interest.

Alkylation of Phenols. The approach used to synthesize commercially available alkylphenols is Friedel-Crafts alkylation. The specific procedure typically uses an alkene as the alkylating agent and an acid catalyst, generally a sulfonic acid. Alkene and catalyst interact to form a carbocation and counter ion (5) which interacts with phenol to form a π complex (6). This complex is held together by the overlap of the filled π-orbital of the aromatic

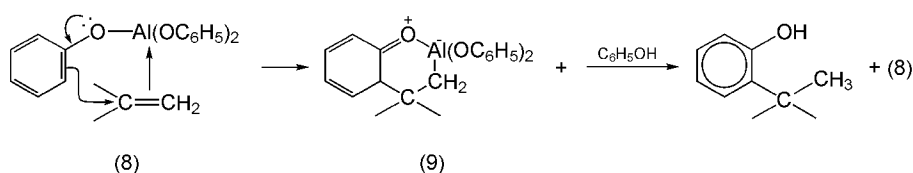
ring with the empty orbital of the carbocation (5). The π -complex can rearrange to the ζ complex (7). Loss of R^+ from complex (7) results in no reaction whereas loss of H^+ results in the alkylation of phenol.



The driving force for the formation of (6) can be viewed as the result of electrostatic interaction, an electron deficient species being attracted to an electron rich species. This type of interaction explains some of the by-products that are formed during these alkylation reactions. Phenylalkyl ethers are the result of an interaction between the unshared electron pairs of the phenol oxygen with the carbocation. Alkene oligomers form when the carbocation complexes with the filled π -orbital of another alkene. These alkene oligomers can in turn react with phenol to produce correspondingly higher molecular weight alkylphenols.

Alkylations of phenol can give rise to three positional isomers, ortho, meta, and para, and multisubstitution products as well. A reaction may yield some of each potential product and this product mix presents a separation problem. Fortunately, judicious choice of catalyst and or reaction conditions allows some control over selectivity. The reactivity of the alkylating agent also controls selectivity. The reaction between phenol and isobutylene [115-11-7], wherein the alkylating agent is the *tert*-butyl carbocation, shows a very high para selectivity using acid catalysis. Tertiary carbocations are the most stable, hence least reactive species and consequently are the most selective. Isomer selectivity in Friedel-Crafts reactions (qv) has also been shown to rely on steric effects, charge distribution, and relative stability of the quinonoid intermediates (6).

In 1957 a procedure was described that selectively alkylated phenol in the ortho position (7). This approach, using aluminum catalysis, made a variety of 2,6-dialkylphenols accessible. The mechanism proposed for this ortho alkylation is outlined as follows:



An aluminum trisphenoxide (8) is generated from phenol and aluminum or a trialkyl aluminum. The attraction between the electropositive aluminum and the electron-rich alkene places the latter in close proximity to the ortho position of the phenol yielding (9). An unreacted phenol molecule can then displace the ortho alkylated phenol. Using an alkene to phenol ratio of 2:1 yields proportionately more 2,6-dialkylphenol. The schematic representation of this reaction is a gross simplification. Some intermolecular alkylation does not take place. The aluminum catalyzed synthesis of 2,6-dialkylphenols generates several isomeric products, albeit in low yields. This procedure works well for making dialkylphenols from alkenes containing up to six carbon atoms. Thereafter, the nonpolar nature of the products and intermediates causes the aluminum trisphenoxide to fall out of solution. Given the bulkiness of the aluminum complex (9), terminal alkenes react more readily than internal alkenes. The use of forcing conditions with internal alkenes presents its own set of problems. At high temperatures the aluminum phenoxide produces a polymeric aluminum species accompanied by the formation of phenyl ethers (8).

The alkylation of phenol with an alkene using either acid or aluminum catalysis probably accounts for 95% of the commercially produced alkylphenols with alkyl groups of three carbons or larger. The alkenes are commercially available and environmentally kind. They do not produce by-products as do alkylations which use alcohols or alkyl halides. Together with an acid catalyst and the appropriate amount of phenol, mono-, di-, and trialkylphenols can be produced.

Several methods are available to supplement the phenol alkylations described above. Primary alkylphenols can be produced using the more traditional Friedel-Crafts reaction. Thus an *n*-butylphenol can be synthesized directly from a butyl halide, phenol, and mild Lewis acid catalyst. Alternatively, butyryl chloride can be used to acylate phenol producing a butyrophenone. Reduction with hydrazine (a Wolff-Kishner reduction) generates butylphenol.

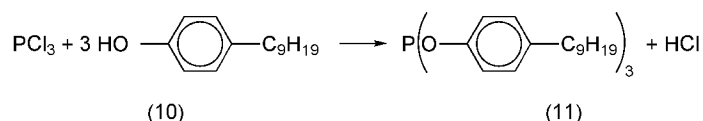
Reactions of Alkylphenols

Alkylphenols undergo a variety of chemical transformations, involving the hydroxyl group or the aromatic nucleus that convert them to value-added products.

THE HYDROXYL GROUP

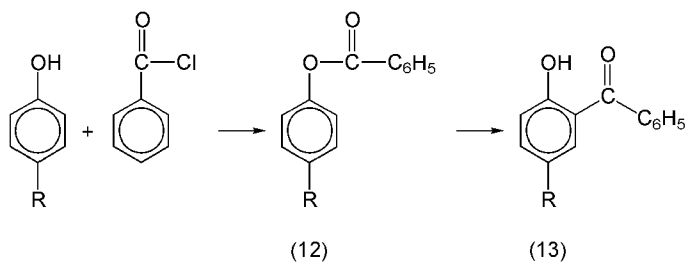
The unshared pairs of electrons on hydroxyl oxygens seek electron deficient centers. Alkylphenols tend to be less nucleophilic than aliphatic alcohols as a direct result of the attraction of the electron density by the aromatic nucleus. The reactivity of the hydroxyl group can be enhanced in spite of the attraction of the ring current by use of a basic catalyst which removes the acidic proton from the hydroxyl group leaving the more nucleophilic alkylphenoxide.

Esterification. Alkylphenols react with acid chlorides and acids to produce commercially important esters. Three equivalents of *p*-nonylphenol (10) react with phosphorus trichloride or tributyl phosphite to produce tris(4-nonylphenyl) phosphite (TNPP) (11).

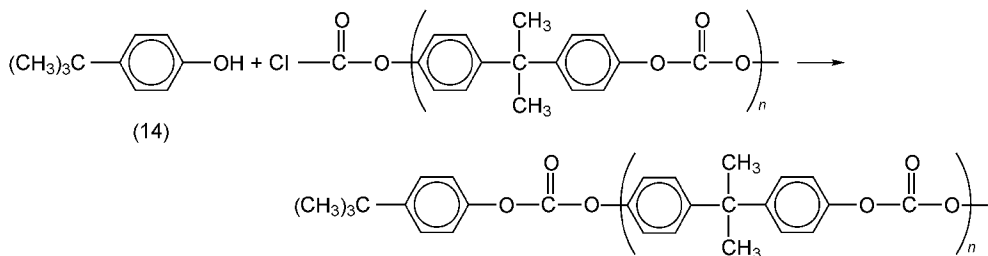


When the phenol reactant is 2,4-di-*tert*-butylphenol, a phosphite ester with greater hydrolytic stability is produced.

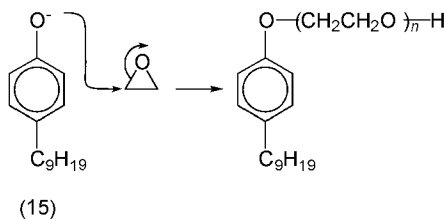
Alkylphenyl esters (12) of aromatic carboxylic acids can be made from appropriate acid chlorides or by transesterification of benzoate esters. The resulting alkylphenyl benzoates undergo a transformation called the Fries rearrangement which involves cleavage of the ester linkage followed by the migration of the benzoyl group to the ortho or para position of the phenol. The reaction can be catalyzed by metal halides in a typical Friedel-Crafts reaction or the process can be photochemical, ie, the photo-Fries. The resulting product is a hydroxybenzophenone (13). These benzophenones have found applicability as uv absorbers in thermoplastics.



Alkylphenols have been substituted for phenol as chain terminators in polycarbonates. In this role, PTBP (14) competes with the diol monomer for reactive chlorocarbonate sites. The ratio of butylphenol to diol controls the molecular weight of the polymer.



Etherification. Many of the monoalkylphenols and some of the dialkylphenols are converted into ethoxylates which find commercial application as nonionic surfactants (9). For example, *p*-nonylphenol reacts with ethylene oxide under mild basic conditions.

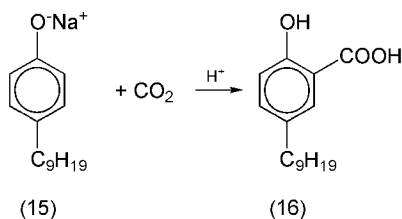


The number of ethylene oxide units added to the phenoxide depends on the application of the ethoxylate. This chemistry is closely related to the reaction between an alkylphenol and epichlorohydrin which is used in epoxy resins (qv).

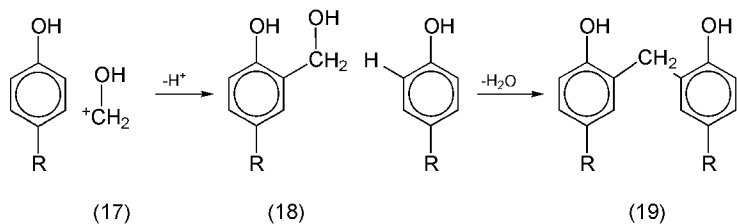
REACTIONS INVOLVING THE RING

The aromatic nucleus of alkylphenols can undergo a variety of aromatic electrophilic substitutions. Electron density from the hydroxyl group is fed into the ring. Besides activating the aromatic nucleus, the hydroxyl group controls the orientation of the incoming electrophile.

Alkylphenols undergo a carboxylation reaction known as the Kolbe Schmidt reaction. In the following example, the phenolate anion of *p*-nonylphenol (15) reacts with carbon dioxide under pressure. Neutralization generates a salicylic acid (16) (10).

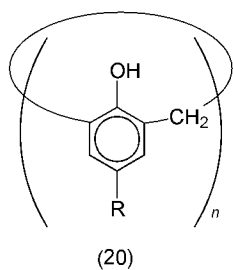


Reactions with Aldehydes and Ketones. An important use for alkylphenols is in phenol-formaldehyde resins. These resins are classified as resoles or novolaks (see PHENOLIC RESINS). Resoles are produced when one or more moles of formaldehyde react with one mole of phenol under basic catalysis. These resins are thermosets. Novolaks are thermoplastic resins formed when an excess of phenol reacts with formaldehyde under acidic conditions. The acid protonates formaldehyde to generate the alkylating electrophile (17).



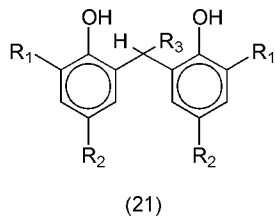
The intermediate methylol derivative (18) is unstable under the reaction conditions and generates an electrophile that undergoes another substitution reaction resulting in the methylene bridge between alkylphenol groups (19). This reaction is repeated to propagate the polymer chain. The choice of alkylphenol as well as the alkylphenol:formaldehyde ratio allows a good deal of control over the properties of the resulting resin.

A newer development in alkylphenol-formaldehyde resins has been the application of this condensation reaction to produce calixarenes, cyclic oligomers of methylene-bridged alkylphenols (20). The smallest cyclic oligomer that has been isolated to date contains four alkylphenol groups.



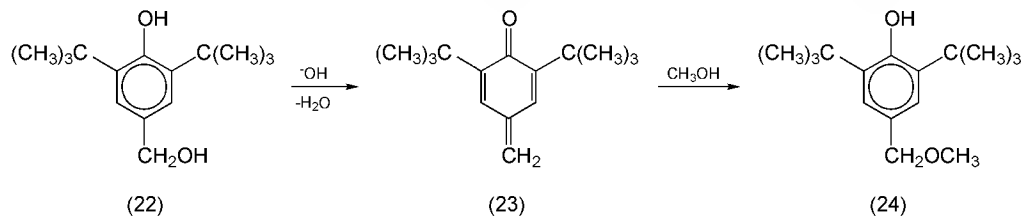
These molecules are significant in the field of research devoted to host–guest complexation. Synthetic routes to a number of calixarenes have been developed (11).

2,4-Dialkylphenols react with aldehydes similarly. A bisphenol (21) is formed by the condensation.



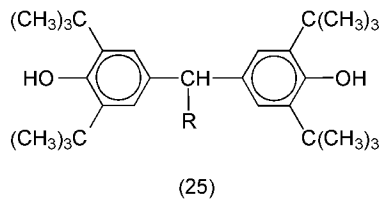
Commercial application of this type of reaction is used to produce 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) ($R^1 = \textit{tert}$ -butyl; $R^2 = \text{methyl}$; $R^3 = \text{H}$) and 2,2'-ethyldienebis(4,6-di-*tert*-butylphenol) ($R^1 = R^2 = \textit{tert}$ -butyl; $R^3 = \text{CH}_3$).

Quinone Methides. The reaction between aldehydes and alkylphenols can also be base-catalyzed. Under mild conditions, 2,6-DTBP reacts with formaldehyde in the presence of a base to produce the methylol derivative (22) which reacts further with base to eliminate a molecule of water and form a reactive intermediate, the quinone methide (23). Quinone methides undergo a broad array of transformations by way of addition reactions. These molecules are conjugated homologues of vinyl ketones, but are more reactive because of the driving force associated with rearomatization after addition. An example of this type of addition is between the quinone methide and methanol to produce the substituted benzyl methyl ether (24).

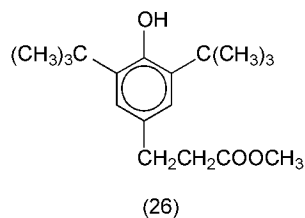


This addition is general, extending to nitrogen, oxygen, carbon, and sulfur nucleophiles. This reactivity of the quinone methide (23) is applied in the synthesis of a variety of stabilizers for plastics. The presence of two *tert*-butyl groups ortho to the hydroxyl group, is the structural feature responsible for the antioxidant activity that these molecules exhibit (see ANTIOXIDANTS).

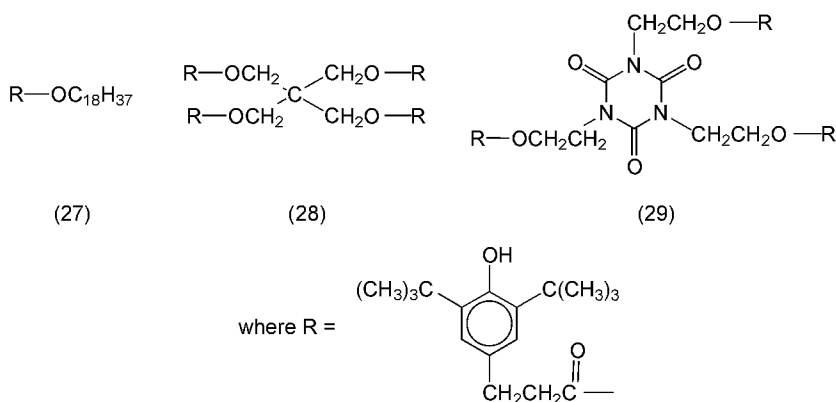
4,4'-Methylenebis(2,6-di-*tert*-butylphenol) (25) ($R = \text{H}$) [118-82-1], the reaction product of two molecules of 2,6-DTBP with formaldehyde under basic conditions, is a bisphenolic antioxidant. The quinone methide in this case is generated *in situ*. The product results from the addition of 2,6-di-*tert*-butylphenolate to (23) (12).



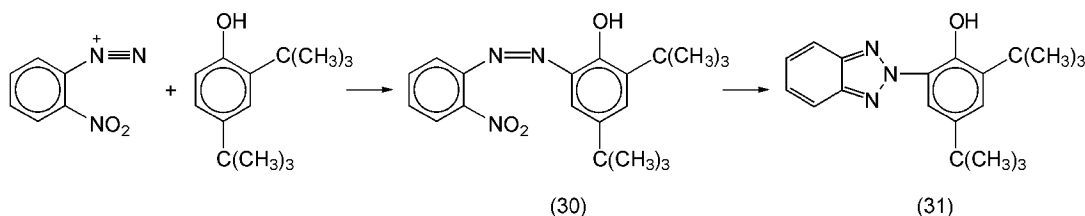
The versatility of this reaction is extended to a variety of aldehydes. The bisphenol derived from 2,6-di-*tert*-butylphenol and furfural, (25) where $R = \text{furfuryl}$ (13), is also used as an antioxidant. The utility of the 3,5-di-*tert*-butyl-4-hydroxybenzyl moiety is evident in stabilizers of all types (14), and its effectiveness has spurred investigations of derivatives of hindered alkylphenols to achieve better stabilizing qualities. Another example is the Michael addition of 2,6-di-*tert*-butyl phenol to methyl acrylate. This reaction is carried out under basic conditions and yields methyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate [6386-38-5] (26) (15).



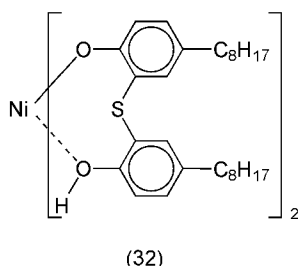
Transesterification reactions between the methyl propionate and various alcohols produce another family of stabilizers. Stearyl alcohol yields octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (27) (16), pentaerythritol gives the tetrakis ester (28) (17), and trishydroxyethyl isocyanurate gives (29) (18).



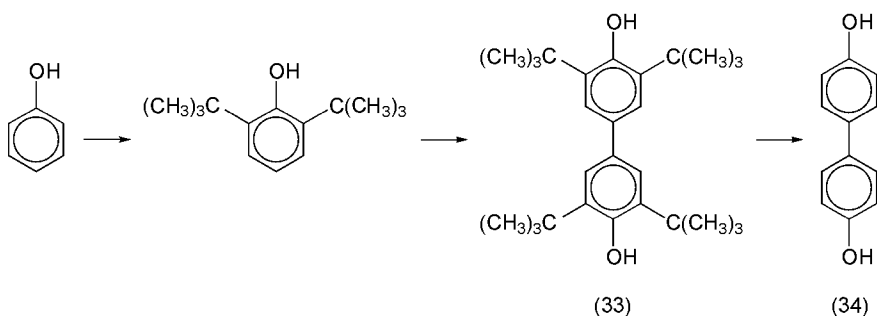
Diazo Coupling Reactions. Alkylphenols undergo a coupling reaction with diazonium salts which is the basis for the preparation of a class of uv light stabilizers for polymers. The interaction of *ortho*-nitrobenzenediazonium chloride with 2,4-di-*tert*-butylphenol results in an azo-coupled product (30). Reduction of the nitro group followed by *in situ* cyclization affords the benzotriazole (31) (19).



Benzotriazoles stabilize resins based on their ability to absorb uv radiation and re-emit the energy as thermal energy through molecular vibrations. Nickel-containing light stabilizers can act as both absorbers and quenchers of excited states of carbonyl impurities (20). One such nickel-containing stabilizer is made by coupling 4-*tert*-octylphenol with sulfur dichloride. The resulting bisphenol-sulfide is used to complex nickel(II) and form (32) (21).



Removal of *tert*-Alkyl Groups. *tert*-Alkyl groups on a phenol nucleus can be removed selectively to produce a desired synthetic result. The oxidative coupling of phenol offers a good example. 2,6-Di-*tert*-butylphenol can be coupled under oxidative conditions to 3,3',5,5'-tetra-*tert*-butyl-4,4'-dihydroxybiphenyl (33). The *tert*-butyl groups can then be removed under acid conditions and recovered as isobutylene. The net result is the formation of 4,4'-dihydroxybiphenyl (34) from phenol (22).



Manufacture and Processing Alkylphenols of commercial importance are generally manufactured by the reaction of an alkene with phenol in the presence of an acid catalyst. The alkenes used vary from single species, such as isobutylene, to complicated mixtures, such as propylene tetramer (dodecene). The alkene reacts with phenol to produce monoalkylphenols, dialkylphenols, and trialkylphenols. The monoalkylphenols comprise ~85% of all alkylphenol production.

The choice of catalyst is based primarily on economic effects and product purity requirements. More recently, the handling of waste associated with the choice of catalyst has become an important factor in the economic evaluation. Catalysts that produce less waste and more easily handled waste by-products are strongly preferred by alkylphenol producers. Some commonly used catalysts are sulfuric acid, boron trifluoride, aluminum phenoxide, methanesulfonic acid, toluene-xylene sulfonic acid, cationic-exchange resin, acidic clays, and modified zeolites.

To describe the varied processes by which alkylphenols are produced, it is convenient to consider the reaction and recovery separately. In some cases this distinction is artificial because the operations are intimately linked, but in many processes the break is operationally significant.

Reactors. Reactors used to produce alkylphenols are simple batch reactors, complex batch reactors, and continuous reactors. All of these reactors have good mixing and heat removal capability. Good mixing is required for contacting the alkene and catalyst with the phenol. Typically, alkene-alkene reactions compete with phenol-alkene reactions at operating conditions. Good mixing minimizes locally high alkene concentrations and thus favors the desired reactions relative to the undesired ones. Good heat removal capability is needed to maintain controlled temperatures because of the highly exothermic nature of these reactions. The selectivity of alkylation is greatly affected by temperature (23).

The simple batch reactor generally consists of a cooled, agitated mixing tank. Figure 1 shows one type of simple batch reactor arrangement. There are four basic operating steps for this type of reactor in alkylphenol service: (1) the phenol is loaded; (2) the catalyst is loaded; (This step may be avoided if an appropriate heterogeneous catalyst is available.) (3) the alkene is loaded at such a rate that the reactor's heat removal capability is not exceeded and the desired reaction temperature is maintained; and (4) the alkylate is removed. This final step is trivial if a homogeneous catalyst is used, but it may require special equipment design if a heterogeneous catalyst is used.

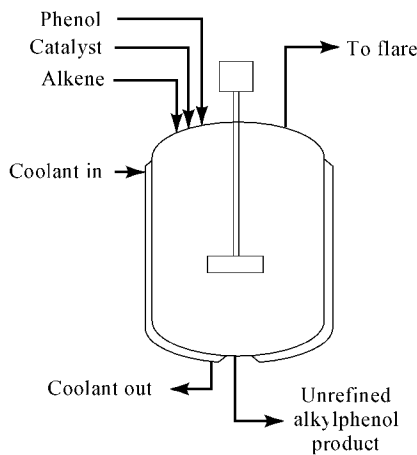


Fig. 1. Flow sheet of simple batch reactor.

The relatively low capital cost of the simple batch reactor is its most enticing feature. The inability to operate under pressure typically limits the simple batch reactor to use with the higher alkenes; ie, octenes, nonenes, and dodecenes. For mainly economic reasons, these reactors are usually run at phenol to alkene mole ratios of between 0.9 and 1.1 to 1.

The complex batch reactor is a specialized pressure vessel with excellent heat transfer and gas liquid contacting capability. These reactors are becoming more common in alkylphenol production, mainly due to their high efficiency and flexibility of operation. Figure 2 shows one arrangement for a complex batch reactor. Complex batch reactors produce the more difficult to make alkylphenols; they also produce some conventional alkylphenols through improved processes.

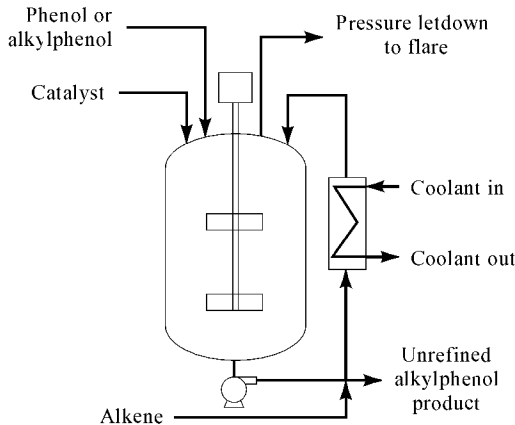


Fig. 2. Flow sheet of complex batch reactor.

The same four operating steps are used with the complex batch reactor as with the simple batch reactor. The powerful capabilities of the complex batch reactor offset their relatively high capital cost. These reactors can operate at phenol to alkene mole ratios from 0.3 to 1 and up. This ability is achieved by designing for positive pressure operation, typically 200 to 2000 kPa (30 to 300 psig), and for the use of highly selective catalysts. Because these reactors can operate at low phenol to alkene mole ratios, they are ideal for production of di- and trialkylphenols.

Among continuous reactors, the dominant system used to produce parasubstituted alkylphenols is a fixed-bed reactor holding a solid acid catalyst. Figure 3 shows an example of this type of reactor. The phenol and alkene are premixed and heated or cooled to the desired feed temperature. This mix is fed to the reactor where it contacts the porous solid, acid-impregnated catalyst. A key design consideration for this type of reactor is the removal of the heat of reaction.

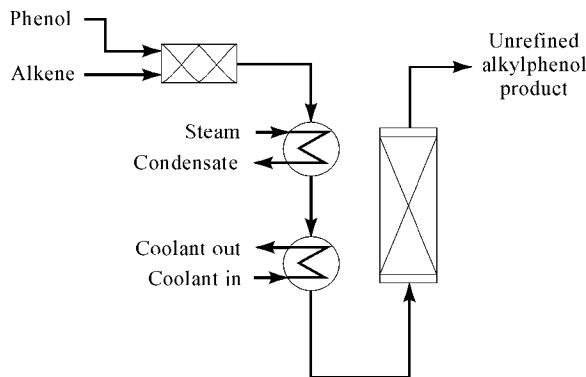


Fig. 3. Flow sheet of continuous reactor.

Phenol and alkenes react quite exothermically. The reaction between 1 mole of phenol and 1 mole of isobutylene to yield 1 mole of *p-tert*-butylphenol PTBP liberates approximately 79.8 kJ mol (19.1 kcal mol) (24). In an adiabatic system, this reaction, if started at 40°C, would result in a reaction product at about 250°C. Temperatures above 200°C are considered unacceptably high in the reactor so design measures are employed to keep the temperature down.

The most common approach to maintaining the desired reaction temperature is to operate with a significant excess of phenol in the reactor. An adiabatic reactor fed with 2 moles of phenol and 1 mole of isobutylene at 40°C would reach about 180°C if all the isobutylene formed PTBP. The selectivity towards the desired monoalkylphenol product almost always improves as the phenol to alkene mole ratio increases. These gains must be weighed

against the higher costs associated with higher mole ratio operation. Both the capital cost and the operating costs increase as the mole ratio is increased, since larger equipment that consumes more energy is needed to separate the excess phenol from the unrefined alkylphenol stream.

Purification. The method used to recover the desired alkylphenol product from the reactor output is highly dependent on the downstream use of the product and the physical properties of the alkylphenol. The downstream uses vary enormously; some require no refining of the alkylphenol feedstock; others require very high purity materials. Physical property differences affect both the basic type of process used for recovery and the operating conditions used within that process.

Some alkylphenol applications can tolerate "as is" reactor products, most significantly in the production of alkylphenol-formaldehyde resins. These resins can tolerate some of the reactant and by-product from the alkylphenol reactor because they undergo purification steps. This resin production route has both capital and operating cost advantages over using purer alkylphenol streams as feedstock. For these savings, the resin producer must operate the process in such a way as to tolerate a more widely varying feedstock and assume the burden of waste disposal of some unreactive materials from the alkylphenol process.

Most alkylphenols sold today require refinement. Distillation is by far the most common separation route. Multiple distillation tower separations are used to recover over 80% of the alkylphenol products in North America. Figure 4 shows a basic alkylphenol distillation train. Excess phenol is removed from the unrefined alkylphenol stream in the first tower. The by-products, which are less volatile than phenol but more volatile than the product, are removed in the second tower. The product comes off the third tower overhead while the heavy by-products come out the bottom.

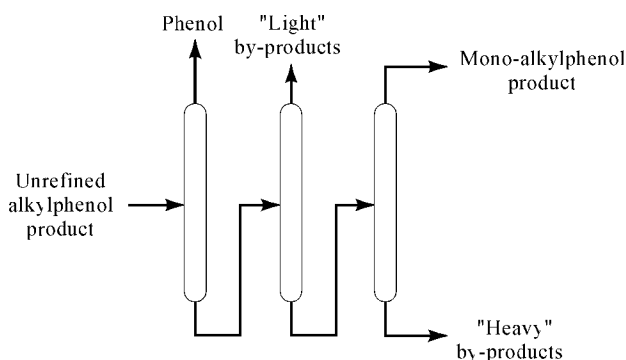


Fig. 4. Monoalkylphenol distillation train.

The design of these distillation systems and the operating conditions used depend on the physical properties of the alkylphenols involved and on the product requirements. Essentially all alkylphenol distillation systems operate under vacuum, but the actual pressures maintained vary considerably. Vacuum operation allows reasonable reboiler temperatures (200–350°C) so that thermal dealkylation reactions of the alkylphenols are slow.

Some alkylphenols in commercial production have low vapor pressures and/or low thermal decomposition temperatures. For these products, the economics of distillation are poor and other recovery processes are used. Crystallization from a solvent is the most common nondistillation method for the purification of these alkylphenols.

Production and Shipment

Most commercially important alkylphenol production is of three types, unrefined alkylphenols, monoalkylphenols, and dialkylphenols. Together, these processes comprise over 95% of all alkylphenol production in the United States. The boundaries between types of production are not rigid; and some commercially important production is through a combination of these processes.

Unrefined alkylphenols are generally produced in the simple batch reactors described earlier. An alkene with between 8 and 12 carbon atoms reacts with phenol to produce a mixture of reactants, monoalkylphenols, and dialkylphenols. These mixtures usually do not freeze above 25°C and so are liquid at production and storage conditions. The product is generally used in the same factory or complex in which it is produced so shipment typically consists of pumping the material from the reactor to a storage tank.

Monoalkylphenols are generally produced in specialized plants that have both continuous reactors and continuous vacuum distillation trains. Alkenes with between 4 and 24 carbon atoms react with phenol to produce an unrefined phenol-alkylphenol mixture. This mixture is fed to the distillation train where the phenol is removed for recycle and the product is isolated. The product is then stored in heated tanks made of stainless steel or phenolic resin lined carbon steel. These tanks are blanketed with inert gas to avoid product discoloration associated with oxidation.

Large volumes of monoalkylphenols are shipped in liquid form by railcar, tank wagon, or export container. These shipping vessels must be stainless steel or phenolic resin lined carbon steel. For smaller volumes, drums and tote-tanks are used. For high freezing point alkylphenols, such as PTBP, the product is flaked and shipped in either bags or supersacs. For low freezing point products, such as *p*-nonylphenol (PNP) (fp < 20°C), the product is shipped in drums or tote-tanks.

Dialkylphenols are also produced in specialized plants. These plants combine complex batch reactors with vacuum distillation trains or other recovery systems. Alkenes with carbon numbers between 4 and 9 react with phenol to make an unrefined alkylphenol mixture, which is fed into the recovery section where very high purity product is isolated. The product is stored, handled, and shipped just as are the monoalkylphenols.

Economic Aspects

Among the key variables in strategic alkylphenol planning are feedstock quality and availability, equipment capability, environmental needs, and product quality. In the past decade, environmental needs have grown enormously in their effect on economic decisions. The manufacturing cost of alkylphenols includes raw-material cost, nonraw-material variable cost, fixed cost, and depreciation.

Raw-material costs are the largest cost items over the lifetime of a plant and typically make up between 40 and 90% of the total manufacturing cost. The placement of plants near production facilities making alkenes and/or phenol is important to producers of alkylphenols. The raw-material costs are so important that a large fluctuation in a raw material price can drive a product from a reasonably profitable situation to a clearly unprofitable one.

Nonraw-material variable costs consist largely of utility costs, but other costs can be significant in this area. For example, operating costs for additional waste treatment are in this category. Nonraw-material variable costs account for 5–20% of the total manufacturing cost of an alkylphenol operation.

Fixed costs include corporate overhead and administration costs as well as those plant-related costs that do not vary with production and contribute 5 to 30% of the total manufacturing cost.

Depreciation costs can drop from as high as 50% of the total manufacturing cost to less than 10% as the plant ages. The effect of the changing depreciation rates is tempered if after-tax analysis is used.

Health and Safety Factors

As a class of compounds the toxicity of alkylphenols range from moderately toxic (oral rat LD₅₀ 50–500 mg/kg) to practically nontoxic (oral rat LD₅₀

5,000–15,000 mg kg) and most are irritants or corrosive toward skin (Table 2). Sensitization to alkylphenols has been reported. 4-*tert*-Butylphenol is known to cause leucoderma (depigmentation of the skin) in sensitive individuals. In general, precautions should be taken when handling alkylphenols to avoid contact with the skin by wearing appropriate protective gloves, clothing, and a face shield or goggles. Alkylphenols should only be stored and handled in well-ventilated areas and appropriate respiration equipment with carbon filters should be worn if PEL or TLV limits are exceeded.

Table 2. Health and Safety Data ^a

Name	CAS Registry Number	RTECS NO. ^b	Irritation data		Toxicity data		
			Skin (rabbit)	Eye (rabbit)	Oral (rat) LD ₅₀ , mg kg	Skin (rabbit) LD ₅₀ , mg kg	Dot skin corrosiv e
4- <i>tert</i> -amylphenol	[80-46-6]	SM682500 0	open, 100 µg 24 h	severe, 500 mg	1830	2000	yes
4- <i>tert</i> -butylphenol	[98-54-4]	SJ8925000	mild, 500 mg 24 h	severe, 50 µg 24 h	2951	2288	yes
2- <i>sec</i> -butylphenol	[89-72-5]	SJ8920000	severe (2 mg 24 h)	severe, 50 µg 24 h	340	5560	yes
4-cumylphenol	[599-64-4]	SL1942450			1770		yes
4-dodecylphenol	[27193-86-8]	SL367500	severe, 8.0–8.0 24 h	moderate, 33.3 110	2140	5000	yes
4-nonylphenol	[84852-15-3]	SM563000 0	severe, 10 mg 24 h	severe, 50 µg 24 h	1620	2140	yes
4- <i>tert</i> -octylphenol	[140-66-9]	SM962500 0	moderate, 20 mg 24 h	severe, 50 µg 24 h	2160		yes
2,4-di- <i>tert</i> -amylphenol	[25231-47-4]	SL3500000		moderate, 100 mg	330		yes
2,4-d- <i>tert</i> -butylphenol	[96-76-4]	SK826000 0			1500		yes
2,6-di- <i>tert</i> -butylphenol	[128-39-2]	SK826500 0	mild, 0.5 g 24 h	minimal, 100 mg 24 h	>5000		no
2,6-di- <i>sec</i> -butylphenol	[5510-99-6]	SK822500 0	severe, 500 mg 24 h	severe, 50 µg 24 h	1320		yes
2,4-di-cumylphenol	[2772-45-4]						yes
2-methylphenol	[95-48-7]	G0630000 0	severe, 524 mg 24 h	severe, 105 mg	121	620	yes
3-methylphenol	[108-39-4]	G0612500 0	severe, 517 mg 24 h	severe, 103 mg	242	1100	yes
4-methylphenol	[106-44-5]	G0647500 0	severe, 517 mg 24 h	severe, 103 mg	207	750	yes
2,6-dimethylphenol	[576-26-1]	ZE612500 0		severe, 100 mg	296	1000	yes

^a Ref. 25.
^b RTECS Registry of Toxic Effects of Chemical Substances.

Commercial Uses and Derivatives of Alkylphenols

Typical physical properties and assays of the commercially most important alkylphenols in terms of worldwide volume were given in Table 1.

4-*tert*-Amylphenol. *p*-*tert*-Amylphenol (PTAP) or 4-(1,1-dimethylpropyl)phenol is commercially produced by the alkylation of phenol with isoamylenes under acidic catalysis. Isoamylenes are a mixture of 2-methyl-1-butene and 2-methyl-2-butene, which is produced by dehydration of the corresponding alcohol or backcracking of the corresponding methyl ether. The highest purity isoamylenes are available from the backcracking of *tert*-amyl methyl ether (TAME), produced from a C₅ raffinate stream by reaction with methanol under acid catalysis.

The crude product formed from the alkylation of phenol with isoamylenes contains principally 2-*tert*-amylphenol, 4-*tert*-amylphenol, and 2,4-di-*tert*-amylphenol. 4-*tert*-Amylphenol is purified to its typical assay of 99 + % by fractional distillation. 4-*tert*-Amylphenol [80-46-6] is commercially available as a solid, flaked material packaged in paper or plastic bags (25 kg net weight) or as a molten material in tank wagon or railcar quantities.

4-*tert*-Amylphenol is employed as a germicide in cleaning solutions (26), but it is being replaced by environmentally safer quaternary ammonium salts. Another commercial application of 4-*tert*-amylphenol is in phenolic resins (qv) (novolaks and resoles). These resins are used in paints and varnishes and as printing ink resins. The ethoxylated novolaks are used as oil field demulsifiers. Because of the high cost of 4-*tert*-amylphenol, which is related to the high cost of isoamylenes, many of the resin applications have been reformulated using 4-*tert*-butylphenol. 4-*tert*-Amylphenol is also used as a vulcanizing agent as the disulfide derivative for the curing of rubber. The worldwide demand and prices for 4-*tert*-amylphenol are shown in Table 3.

Table 3. Worldwide Demand and Prices for Alkylphenols

Alkylphenol	Worldwide demand, t	U.S. demand ^a , t	Truckload quantities of flaked materials, \$ kg	Bulk quantities of molten materials, \$ kg
4- <i>tert</i> -amylphenol	1,360–1,590	455	2.6	2.51
4- <i>tert</i> -butylphenol	38,600–40,900		2.09 ^b 2.27 ^c	2.00 ^b 2.18 ^c
2- <i>sec</i> -butylphenol	4,090–5,000	909	1.98 ^d	1.85 ^e
4-cumylphenol	1,360–1,820	909		2.75 ^e
4-dodecylphenol			1.69 ^d	1.54 ^e
2-methylphenol	36,400–45,500	^f	1.39 ^d	1.28 ^e
3-methylphenol	18,200–20,450	2,270–3,640	3.76 ^d	3.63 ^e

4-methylphenol	31,800–34,100	f	2.79 ^d	2.86
4-nonylphenol	182,000–205,000		1.58 ^d	1.45 ^e
4- <i>tert</i> -octylphenol	22,700–27,300		2.27 ^b	2.18 ^b
			2.31 ^c	2.22 ^c
2,4-di- <i>tert</i> -amylphenol	1,820–2,270		2.97	2.82 ^e
2,4-di- <i>tert</i> -butylphenol	4,090–4,550		2.68	2.53 ^e
2,6-di- <i>tert</i> -butylphenol	27,300–29,500		2.66 ^d	2.51 ^e
di- <i>sec</i> - <i>tert</i> -butylphenol	455–909	g	2.35	2.20 ^e
2,4-dicumylphenol	455–909		5.72 ^d	5.50 ^e
2,6-dimethylphenol	90,900–114,000			1.98 ^e

^a Approximately 1–2 the worldwide demand unless otherwise noted.

^b Technical grade.

^c High purity.

^d Of drums.

^e Bulk shipments in tank wagons or railcars.

^f Approximately 1–3 the worldwide demand.

^g Most demand in the United States.

4-*tert*-Butylphenol. *p*-*tert*-Butylphenol (PTBP) or 4-(1,1-dimethylethyl)phenol is produced from the alkylation of phenol with isobutylene under acid catalysis. Isobutylene [115-11-7] is commercially produced mostly from the dehydration of *tert*-butyl alcohol or from the cracking of methyl *tert*-butyl ether (MTBE). The principal products of this alkylation are 2-*tert*-butylphenol, 4-*tert*-butylphenol, 2,4-di-*tert*-butylphenol, and minor amounts of 2,4,6-tri-*tert*-butylphenol and 4-*tert*-octylphenol. 4-*tert*-Butylphenol is available in a technical grade which is used in the production of phenolic resins. A high purity grade is available for the production of glycidyl ethers and for the chain termination of polycarbonates. 4-*tert*-Butylphenol [98-54-4] is available as a flaked solid packaged in paper or plastic bags (25 kg net weight), and as a molten material in tankwagon and railcar quantities.

Phenolic resin applications account for 60–70% of all 4-*tert*-butylphenol consumed worldwide. These resins are used in a wide range of applications which include paints, coating resins, and printing inks (27). 4-*tert*-Butylphenol novolak resins react with ethylene oxide to form oil field demulsifiers or are converted into phosphate esters for use as hydraulic fluids and synthetic lubricants. 4-*tert*-Butylphenol resoles react with alkaline-earth metal hydroxides to produce metal resinsates. The resinates are combined with a rubber component to give an adhesive. Other uses of 4-*tert*-butylphenol include the chain termination of polycarbonates where its use in the place of phenol gives a polycarbonate with better heat distortion characteristics and improved processability for injection grade material. 4-*tert*-Butylphenol is converted to its corresponding glycidyl ether by the reaction with epichlorohydrin followed by dehydrohalogenation. The glycidyl ether is used as a hardner in epoxy resins (qv). 4-*tert*-Butylphenol can be reduced with hydrogen to a mixture of *cis*-4-*tert*-butylcyclohexanol and *trans*-4-*tert*-butylcyclohexanol under nickel catalysis. The corresponding acetate derivative is widely used as a perfume in soaps and detergents. The sodium salt of the phosphoric ester of 4-*tert*-butylphenol, sodium bis(4-*tert*-butylphenyl) phosphate, is used as a nucleating agent for polypropylene (28). The use of a nucleator provides a polypropylene with improved thermal properties and increased clarity. 4-*tert*-Butylphenol is used in the production of pesticides such as 2-(4-*tert*-butylphenoxy)cyclohexyl-2-propynyl sulfide [2312-35-8], which is used on a variety of fruits and vegetables (29).

The consumption of 4-*tert*-butylphenol in the production of phenolic resins represents an application in a mature market and little growth is projected. Its use in end-capping polycarbonates, in the production of glycidyl ethers, and in the production of nucleation agents for polypropylene is expected to grow at a rate above the growth of the GNP (see Table 3).

2-*sec*-Butylphenol. *o*-*sec*-Butylphenol (OSBP) or 2-(1-methylpropyl)phenol is produced by the alkylation of phenol with butene under aluminum or acid catalysis. The aluminum catalysis route selectively yields 2-*sec*-butylphenol whereas the acid catalysis route yields a 2:1 mixture of 2-*sec*-butylphenol and 4-*sec*-butylphenol. 2-*sec*-Butylphenol [89-72-5] is a liquid available in 55-gal drums (208-L) and in bulk quantities in tank wagons and railcars.

Up until 1986 the major use for 2-*sec*-butylphenol was in the production of the herbicide, 2-*sec*-butyl-4,6-dinitrophenol [88-85-7], which was used as a pre- and postemergent herbicide and as a defoliant for potatoes (30). The EPA banned its use in October 1986 based on a European study which showed that workers who came in contact with 2-*sec*-butyl-4,6-dinitrophenol experienced an abnormally high rate of reproduction problems. France and the Netherlands followed with a ban in 1991. A significant volume of 2-*sec*-butyl-4,6-dinitrophenol is used worldwide as a polymerization inhibitor in the production of styrene where it is added to the reboiler of the styrene distillation tower to prevent the formation of polystyrene (31). OSBP is used in the Far East as the carbamate derivative, 2-*sec*-butylphenyl-*N*-methylcarbamate [3766-81-2] (BPMC) (32). BPMC is an insecticide used against leaf hoppers which affect the rice fields.

Because of environmental concerns about 2-*sec*-butylphenol-based derivatives, the market growth is expected to be negative in the future, with the exception of possible significant growth in the use of the carbamate insecticide (see Table 3).

4-Cumylphenol. *p*-Cumylphenol (PCP) or 4-(1-methyl-1-phenylethyl)phenol is produced by the alkylation of phenol with α -methylstyrene under acid catalysis. α -Methylstyrene is a by-product from the production of phenol via the cumene oxidation process. The principal by-products from the production of 4-cumylphenol result from the dimerization and intramolecular alkylation of α -methylstyrene to yield substituted indanes. 4-Cumylphenol [599-64-4] is purified by either fractional distillation or crystallization from a suitable solvent. Purification by crystallization results in the easy separation of the substituted indanes from the product and yields a solid material which is packaged in plastic or paper bags (20 kg net weight). Purification of 4-cumylphenol by fractional distillation yields a product which is almost totally free of any dicumylphenol. The molten product resulting from purification by distillation can be flaked to yield a solid form; however, the solid form of 4-cumylphenol sinters severely over time. PCP is best stored and transported as a molten material.

The major use of 4-cumylphenol is as a chain terminator for polycarbonates. Its use in place of phenol gives a polycarbonate with superior properties (33). For a low molecular weight polycarbonate used for injection-molding applications, the use of 4-cumylphenol as a chain terminator significantly lowers the volatility of the resin. Other uses of 4-cumylphenol include the production of phenolic resins, some of which have applications in the electronics industry (34). Another application of 4-cumylphenol involves its reaction with ethylene oxide to form a specialty surfactant.

The growth rate of 4-cumylphenol is expected to parallel the growth rate of polycarbonates, particularly the grades used to produce compact discs (see Table 3).

4-Dodecylphenol. *p*-Dodecylphenol (PDDP) may be produced by the reaction of phenol with dodecene under acid catalysis, but commercial 4-dodecylphenol is produced from propylene tetramer. Dodecene differs significantly from the idealized tetramer of propylene because of skeletal rearrangements which occur during the oligomerization process, producing a complex mixture of tri- and tetrasubstituted monoolefins. Although dodecene is purified by fractional distillation, it contains olefins with carbon numbers ranging from C₁₀ to C₁₄; the C₁₂ content is typically 60–70%. Two grades of 4-dodecylphenol [27193-86-8] are commercially available. A technical grade of 4-dodecylphenol is a nondistilled product and contains approximately 10% 2-dodecylphenol, 85% 4-dodecylphenol, and 5% 2,4-didodecylphenol. A high purity grade is fractionally distilled and contains approximately 5% 2-dodecylphenol, 95% 4-dodecylphenol, and only a trace of 2,4-didodecylphenol. The technical grade of 4-dodecylphenol is amber in color, whereas the high purity grade is colorless. 4-Dodecylphenol is available in 55-gal drums (208-L) and as bulk shipments in tank wagons and railcars.

The major use of technical grade 4-dodecylphenol is in lube oil additives. 4-Dodecylphenol is converted to a calcium phenolate [50910-68-4] and

used as a detergent in lubricating oils (35). The phenolate combines with combustion debris to prevent the accumulation of the debris on engine parts and neutralizes the strong acids formed during combustion and oxidation. The reaction product of 4-dodecylphenol with ethylene oxide and propylene oxide is used as a corrosion inhibitor in oil. It coats the inner surfaces of an engine to prevent the corrosion of moving parts. 4-Dodecylphenol is used in the production of a zinc dithiophosphate ester [54261-67-5], which is used as an antioxidant and antiwear additive for high temperature applications (36).

High purity 4-dodecylphenol is used to produce specialty surfactants by its reaction with ethylene oxide. The low color of high purity 4-dodecylphenol is important in this application from a standpoint of aesthetics. 4-Dodecylphenol is also used to produce phenolic resins which are used in adhesive applications and printing inks. 4-Dodecylphenol is also used as an epoxy curing catalyst where the addition of 4-dodecylphenol accelerates curing of the epoxy resin to a hard, nontacky solid.

The worldwide consumption of 4-dodecylphenol is difficult to estimate since the majority of 4-dodecylphenol produced is captively used. Prices appear in Table 3. Little growth in the consumption of 4-dodecylphenol is predicted because of the mature nature of the markets of its derivatives.

2-Methylphenol. This phenol, commonly known as *o*-cresol, is produced synthetically by the gas phase alkylation of phenol with methanol using modified alumina catalysis or it may be recovered from naturally occurring petroleum streams and coal tars. Most is produced synthetically. Reaction of phenol with methanol using modified zeolite catalysts is a concerted dehydration of the methanol and alkylation of the aromatic ring. 2-Methylphenol [95-48-7] is available in 55-gal drums (208-L) and in bulk quantities in tank wagons and railcars.

The majority of 2-methylphenol is used in the production of novolak phenolic resins. High purity novolaks based on 2-methylphenol are used in photoresist applications (37). Novolaks based on 2-methylphenol are also epoxidized with epichlorohydrin, yielding epoxy resins after dehydrohalogenation, which are used as encapsulating resins in the electronics industry. Other uses of 2-methylphenol include its conversion to a dinitro compound, 4,6-dinitro-2-methylphenol [534-52-1] (DNOC), which is used as a herbicide (38). DNOC is also used to a limited extent as a polymerization inhibitor in the production of styrene, but this use is expected to decline because of concerns about the toxicity of the dinitro derivative.

2-Methylphenol is converted to 6-*tert*-butyl-2-methylphenol [2219-82-1] by alkylation with isobutylene under aluminum catalysis. A number of phenolic anti-oxidants used to stabilize rubber and plastics against thermal oxidative degradation are based on this compound. The condensation of 6-*tert*-butyl-2-methylphenol with formaldehyde yields 4,4'-methylenebis(2-methyl-6-*tert*-butylphenol) [96-65-1], reaction with sulfur dichloride yields 4,4'-thiobis(2-methyl-6-*tert*-butylphenol) [96-66-2], and reaction with methyl acrylate under base catalysis yields the corresponding hydrocinnamate. Transesterification of the hydrocinnamate with triethylene glycol yields triethylene glycol-bis[3-(3-*tert*-butyl-5-methyl-4-hydroxyphenyl)propionate] [36443-68-2] (39). 2-Methylphenol is also a component of cresylic acids, blends of phenol, cresols, and xlenols. Cresylic acids are used as solvents in a number of coating applications (see Table 3).

3-Methylphenol. *m*-Cresol is produced synthetically from toluene. Toluene is chlorinated and the resulting chlorotoluene is hydrolyzed to a mixture of methylphenols. Purification by distillation gives a mixture of 3-methylphenol and 4-methylphenol since they have nearly identical boiling points. Reaction of this mixture with isobutylene under acid catalysis forms 2,6-di-*tert*-butyl-4-methylphenol and 2,4-di-*tert*-butyl-5-methylphenol, which can then be separated by fractional distillation and debutylated to give the corresponding 3- and 4-methylphenols. A mixture of 3- and 4-methylphenols is also derived from petroleum crude and coal tars.

A major use of 3-methylphenol [108-39-4] is in the production of phenolic based antioxidants which are particularly good at stabilizing polymers in contact with copper against thermal oxidative degradation. The alkylation of 3-methylphenol with isobutylene under acid or aluminum catalysis yields 2-*tert*-butyl-5-methylphenol [88-60-8]. Condensation of 2-*tert*-butyl-5-methylphenol with butyraldehyde yields the corresponding 4,4'-butylidenebis(6-*tert*-butyl-3-methylphenol) [85-60-9] which is used in the stabilization of rubber and latex (40). Condensation of 2-*tert*-butyl-5-methylphenol with crotonaldehyde yields a corresponding trisphenol derivative, 1,1,3-tris(5-*tert*-butyl-2-methyl-4-hydroxyphenyl)butane [1843-03-4], which is used to stabilize polymers for high temperature applications (41). The reaction of 2-*tert*-butyl-5-methylphenol with sulfur dichloride yields 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) [96-69-5] which is widely used in curable rubber.

Another significant use of 3-methylphenol is in the production of herbicides and insecticides. 2-*tert*-Butyl-5-methylphenol is converted to the dinitro acetate derivative, 2-*tert*-butyl-5-methyl-4,6-dinitrophenyl acetate [2487-01-6] which is used as both a pre- and postemergent herbicide to control broad leaf weeds (42). Carbamate derivatives of 3-methylphenol based compounds are used as insecticides. The condensation of 3-methylphenol with formaldehyde yields a curable phenolic resin. Since 3-methylphenol is trifunctional with respect to its reaction with formaldehyde, it is possible to form a thermosetting resin by the reaction of a prepolymer with paraformaldehyde or other suitable formaldehyde sources. 3-Methylphenol is also used in the production of fragrances and flavors. It is reduced with hydrogen under nickel catalysis and the corresponding esters are used as synthetic musk (see Table 3).

4-Methylphenol. *p*-Cresol is produced synthetically from toluene. Toluene is sulfonated to yield *para*-toluenesulfonic acid, which is then converted to 4-methylphenol via the caustic fusion route. A minor amount of 4-methylphenol is also derived from petroleum crude and coal tars. 4-Methylphenol [106-44-5] is available in 55-gal drums (208-L) and in bulk quantities as a molten material.

The bulk of 4-methylphenol is used in the production of phenolic antioxidants. The alkylation of 4-methylphenol with isobutylene under acid catalysis yields 2-*tert*-butyl-4-methylphenol [2409-55-4] and 2,6-di-*tert*-butyl-4-methylphenol [128-37-0]. The former condenses with formaldehyde under acid catalysis to yield 2,2'-methylene bis(6-*tert*-butyl-4-methylphenol) [119-47-1], which is widely used in the stabilization of natural and synthetic rubber (43). The reaction of 2-*tert*-butyl-4-methylphenol with sulfur dichloride yields 2,2'-thiobis(6-*tert*-butyl-4-methylphenol) [90-66-4]. 2,6-Di-*tert*-butyl-4-methylphenol, which is commonly known as BHT (butylated hydroxy toluene), is a widely used phenolic antioxidant in the stabilization of oils, rubber, and polyolefins (44). BHT is also one of the few *phenolic antioxidants* approved by the FDA as a direct food additive where it is used to retard the oxidation of naturally occurring oils in food.

Other uses of 4-methylphenol include its conversion to a benzotriazole uv stabilizer, 2-(2'-hydroxy-5'-methylphenyl)benzotriazole [2440-22-4] (45). The benzotriazole-based uv stabilizer makes possible the extended use of thermoplastics in outdoor applications. Other minor applications for 4-methylphenol include its use in the production of novolak or resole phenolic resins. It is also used in the production of certain dyes and fragrances (Table 3).

4-Nonylphenol. *p*-Nonylphenol (PNP) is produced by the alkylation of phenol with nonene under acid catalysis. All commercially produced PNP is made from nonene based on the trimerization of propylene. Because of the skeletal rearrangements which occur during the oligomerization of propylene, commercial grade nonene does not have a high percentage of the idealized structure, 4,6-dimethyl-2-heptene. Rather it is a complex mixture of olefins, mostly tri- and tetrasubstituted monoolefins. Nonene is fractionally distilled from other oligomers and contains approximately 90° C₉ olefins; the remaining 10° is C₉ and C₁₀ olefins. The two commercial purity grades of 4-nonylphenol are a technical grade which is composed of 10–12° 2-nonylphenol, 85–90° 4-nonylphenol, and up to 5° 2,4-dinonylphenol, and a high purity grade which contains 5° maximum 2-nonylphenol, 95° minimum 4-nonylphenol, and only a trace of 2,4-dinonylphenol. 4-Nonylphenol [84852-15-3] is available in 55-gal drums (280-L) and in bulk quantities in tank wagons and railcars.

The major use for 4-nonylphenol is in the production of nonionic surfactants (10). 4-Nonylphenol reacts with ethylene oxide in a mole ratio that varies from 1–40 under base catalysis. 4-Nonylphenol based nonionic surfactants are the largest volume alkylphenol based ethoxylate with a volume in excess of 136,400 t yr. The most common nonionic surfactant based on 4-nonylphenol is the nine-mole ethoxylate. Higher mole ratios in the range of 12–15 moles of ethylene oxide per mole of 4-nonylphenol are used as emulsifiers for agrochemicals. Other major applications for alkylphenol ethoxylates are as cleaners of metal surfaces; detergents for car washes, commercial laundries, and the rug cleaning industry; as a dispersant for wood pulp in the production of paper, and as an emulsifier in the production of latex paint (46). 4-Nonylphenol based ethoxylates can be converted to phosphate esters or sulfonated to the corresponding sulfate to yield higher performing surfactants. Phosphate esters of 4-nonylphenol are also reported to be excellent flame retardants (47).

Another significant use of 4-nonylphenol is in the production of tris(4-nonylphenyl) phosphite [3050-88-2] (TNPP) (48), a secondary antioxidant which protects organic materials against oxidative degradation by decomposing hydroperoxides. In this process, the hydroperoxide is converted to the corresponding alcohol and the phosphite is converted to the corresponding phosphate. Phosphites form synergistic mixtures with phenolic-based antioxidants. Tris(4-nonylphenyl) phosphite is widely used in the stabilization of natural and synthetic rubber, vinyl polymers, and polyolefins and styrenics;

and it has the distinction of being one of the few commercially available liquid triaryl phosphites. Other uses of 4-nonylphenol include its conversion to barium [41157-58-8] and calcium [100842-25-9] phenolates, which are used as heat stabilizers in poly(vinyl chloride) (49). 4-Nonylphenol also has application as a catalyst in the curing of epoxy resins (50,51). Hydrogen bonding of the acidic proton on the hydroxyl group of 4-nonylphenol with the oxygen of the oxirane ring may assist in the opening of the epoxide.

The worldwide consumption of 4-nonylphenol is somewhat difficult to ascertain because of the captive consumption by some producers, but in Table 3 it is estimated based on derivatives. Future growth in the consumption of 4-nonylphenol is predicted to be in line with the growth rate in the GNP, but some market share in surfactants has been lost to the linear alcohol surfactants because of environmental concerns over aquatic toxicity and biodegradability of alkylphenol based ethoxylates. The use of alkylphenol ethoxylates was banned in Switzerland in 1986 and Germany is undergoing a voluntary phase out by the early 1990s. An industry group of 4-nonylphenol producers and surfactant producers is currently operating under a consent order from EPA to carry out a wide range study on the biodegradability of 4-nonylphenol-based ethoxylates and toxicity studies on aquatic life forms of the resulting break-down products. Early results from testing of sediments from river beds and waste plant sludge show that nonylphenol-based ethoxylates are readily biodegraded and the residual level of 4-nonylphenol is very low.

The use of 4-nonylphenol in the production of tris(4-nonylphenyl) phosphite is also not expected to show much growth because of its replacement in many polymers by higher performing and more hydrolytically stable phosphites.

4-*tert*-Octylphenol. *p-tert*-Octylphenol (PTOP) or 4-(1,1,3,3-tetramethylbutyl)phenol is produced by the alkylation of phenol with diisobutylene under acid catalysis. Diisobutylene is a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene. A small amount of skeletal rearrangement during alkylation leads to a second 4-*tert*-octylphenol isomer which has the proposed structure of 1,1,2,3-tetramethylbutyl as the alkyl radical. The crude alkylation product typically contains 4-*tert*-butylphenol (from the backcracking of the diisobutylene), 2-*tert*-octylphenol, 4-*tert*-octylphenol, butyloctylphenol, and 2,4-dioctylphenol. 4-*tert*-Octylphenol is purified by fractional distillation under reduced pressure; it is available as a technical grade which contains 5–8° o 2-*tert*-octylphenol, 90–95° o 4-*tert*-octylphenol, and 1–2° o butyloctylphenol. A high purity grade is also available which contains less than 2° o 2-*tert*-octylphenol, 98–99° o 4-*tert*-octylphenol, and only a trace of higher boiling alkylphenols. 4-*tert*-Octylphenol [140-66-9] is packaged as a flaked solid in paper or plastic bags (25 kg net weight) or as a molten product for bulk shipments in tank wagons and railcars.

4-*tert*-Octylphenol reacts with ethylene oxide under base catalysis and the resulting ethoxylates are used in many of the same applications as the 4-nonylphenol-based surfactants. The consumption of 4-*tert*-octylphenol-based surfactants in the United States is in excess of 22,700 t yr. A major use area for ethoxylates based on 4-*tert*-octylphenol is as a surfactant in the emulsion polymerization of acrylic and vinyl monomers (52). The 4-*tert*-octylphenol ethoxylate aids in the dispersion of the monomers in the aqueous medium and stabilizes the latex formed as a result of polymerization.

Another important application for 4-*tert*-octylphenol is in the production of phenolic resins. Novolak resins based on 4-*tert*-octylphenol are widely used in the tire industry as tackifiers. The tackiness of these resins binds the many parts of an automobile tire prior to final vulcanization. A specialty use for novolak resins based on 4-*tert*-octylphenol is the production of a zincated resin, which is formulated as a dispersion in water and coated onto paper in combination with encapsulated leuco dyes to yield carbonless copy paper (see MICROENCAPSULATION). Pressure from writing bursts the encapsulated leuco dye, which is converted from its colorless form to its colored form by the *zincated resin* (53). Novolak resins based on 4-*tert*-octylphenol are also used in the production of specialty printing inks.

Resoles based on 4-*tert*-octylphenol react with alkaline-earth metal hydroxides to yield metal resins. The resinate is combined with natural or synthetic rubber to produce an adhesive. The 4-*tert*-octylphenol-based resin gives the adhesive its initial tack which holds the two surfaces undergoing bonding together while the other components of the adhesive undergo final curing.

Other applications for 4-*tert*-octylphenol include chain termination of polycarbonates (54). The properties of low molecular weight polycarbonates used in injection-molding applications to form compact disks are enhanced when the polymer is terminated using 4-*tert*-octylphenol.

Another use of 4-*tert*-octylphenol is in the production of uv stabilizers. 4-*tert*-Octylphenol reacts with sulfur dichloride to yield the thio-bisphenol derivative, which then reacts with nickel acetate to form 2,2'-thiobis(4-*tert*-octylphenolate)-*N*-butylamine nickel [14516-71-3]. This type of stabilizer is widely used in the production of outdoor carpeting based on polypropylene fibers. Nickel compounds give a green discoloration which limits their applications. A second class of uv stabilizers based on the benzotriazole structure. 2-(2'-hydroxy-5'-*tert*-octylphenyl)benzotriazole [3147-75-9] is produced from 4-*tert*-octylphenol (55).

It is difficult to estimate the world consumption of 4-*tert*-octylphenol because a significant volume is captively consumed as a crude alkylphenol by producers of phenolic resins. The best estimates are given in Table 3. The overall growth rate of 4-*tert*-octylphenol is expected to track the growth in the GNP. As with 4-nonylphenol-based surfactant, the surfactants based on 4-*tert*-octylphenol have also lost market share to the linear alcohol ethoxylates because of concerns over biodegradability and product aquatic toxicity. The use of 4-*tert*-octylphenol in the production of phenolic resins is a mature market and little growth is forecasted. However, the use of 4-*tert*-octylphenol in the chain termination of polycarbonates and in the production of uv stabilizers is expected to have an above average growth rate.

Dialkylated Phenols. 2,4-Di-*tert*-amylphenol (2,4-DTAP) or 2,4-bis(1,1-dimethylpropyl)phenol is produced by the alkylation of phenol with isoamylene under acid catalysis in a mole ratio of 2:1 (isoamylene to phenol). The crude alkylation product contains 4-*tert*-amylphenol, 2,4-di-*tert*-amylphenol, and 2,4,6-tri-*tert*-amylphenol. The 2,4-di-*tert*-amylphenol is purified via fractional distillation under reduced pressure. 2,4-Di-*tert*-amylphenol [25231-47-4] is available in 55-gal drums (208-L) and bulk quantities in tank wagon and railcar shipments.

A major use for 2,4-di-*tert*-amylphenol is in the production of uv stabilizers; the principal one is a benzotriazole-based uv absorber, 2-(2'-hydroxy-3',5'-di-*tert*-amylphenyl)-5-chlorobenzotriazole [25973-55-1], which is widely used in polyolefin films, outdoor furniture, and clear coat automotive finishes (56). Another significant use for 2,4-di-*tert*-amylphenol is in the photographic industry. A number of phenoxyacetic acid derivatives of 2,4-di-*tert*-amylphenol are used as developing agents in color photography (qv) (57). Other uses include its reaction with ethylene oxide under base catalysis to form a specialty surfactant used to treat cotton fibers to prevent the redeposition of dirt onto the fibers during the production of cotton-based fabric. A phenoxy poly(ethylene oxide) based on 2,4-di-*tert*-amylphenol also has an application as a fuel additive where it is used as a corrosion inhibitor.

The growth rate for 2,4-di-*tert*-amylphenol is predicted to be above GNP growth rate, mainly driven by the use of the benzotriazole derivative as a uv stabilizer for clear-coat applications in auto finishes (see Table 3).

2,4-Di-*tert*-butylphenol (2,4-DTBP) or 2,4-bis(1,1-dimethylethyl)phenol is produced by the alkylation of phenol with isobutylene under acid catalysis using a mole ratio of 2:1 (isobutylene to phenol). The crude product contains 4-*tert*-butylphenol, 2,4-di-*tert*-butylphenol, and 2,4,6-tri-*tert*-butylphenol. The 2,4-*tert*-butylphenol is purified by fractional distillation under reduced pressure. 2,4-Di-*tert*-butylphenol [96-76-4] is available in 55-gal drums (208-L) and in bulk as a molten material.

The primary use for 2,4-di-*tert*-butylphenol is in the production of substituted triaryl phosphites. 2,4-Di-*tert*-butylphenol reacts with phosphorus trichloride typically using a trialkylamine or quaternary ammonium salt as the catalyst. Hydrogen chloride is formed and either complexed with the amine or liberated as free hydrogen chloride gas forming the phosphite ester, tris(2,4-di-*tert*-butylphenyl)phosphite [31570-04-4] (58). The phosphite-based on 2,4-di-*tert*-butylphenol is a solid and very hydrolytically stable. Because of this hydrolytic stability it has replaced the use of tris(4-nonylphenyl) phosphite and other less stable phosphites in polyolefins and engineering resins. Another secondary antioxidant based on 2,4-di-*tert*-butylphenol is the diphosphite derived from pentaerythritol, bis(2,4-di-*tert*-butylphenyl)pentaerythrityl diphosphite [26741-53-7] (59). It too is widely used in polyolefins, and in engineering resins where high performance is required. 2,4-Di-*tert*-butylphenol is also used in the production of a benzotriazole-based uv stabilizer, 2-(2'-hydroxy-3',5'-di-*tert*-butylphenyl)-5-chlorobenzotriazole [3864-99-1]. Another uv stabilizer is the phenyl ester based on the carboxylic acid of 2,6-di-*tert*-butylphenol, 2,4-di-*tert*-butylphenyl 3',5'-di-*tert*-butyl-4'-hydroxybenzoate [4221-80-1] (60). 2,4-Di-*tert*-butylphenol condenses with acetaldehyde under acid catalysis to produce a phenolic-based primary antioxidant, 2,2'-ethylidenebis(4,6-di-*tert*-butylphenol) [35958-30-6] which is used in the stabilization of polyolefins, styrenics, synthetic and natural rubber against thermal oxidative degradation.

The growth rate for 2,4-di-*tert*-butylphenol is estimated to be above average as the market share for high performance phosphites increase (see Table 3).

2,6-Di-*tert*-butylphenol (2,6-DTBP) or 2,6-bis(1,1-dimethylethyl)phenol is produced from phenol by alkylation with isobutylene under aluminum

catalysis. The crude alkylated phenol contains 2-*tert*-butylphenol, 2,6-di-*tert*-butylphenol, and 2,4,6-tri-*tert*-butylphenol. Pure 2,6-di-*tert*-butylphenol is produced by vacuum fractional distillation. Aluminum trisphenoxide is very selective in the formation of 2,6-di-*tert*-butylphenol and yields in excess of 80% are possible. 2,6-Di-*tert*-butylphenol [128-39-2] is packaged in 55-gal drums (208-L) and sold as a molten material in bulk quantity shipments in tank wagons and railcars.

The principal use for 2,6-di-*tert*-butylphenol is in the production of hindered phenolic antioxidants and this application accounts for 80–90% of all of this compound produced. Reaction of 2,6-DTBP with formaldehyde under base catalysis forms the methylene bisphenolic, 4,4'-methylenebis(2,6-di-*tert*-butylphenol) [118-82-1] which is used as a primary antioxidant in the stabilization of greases (61). In an excess of formaldehyde the hydroxymethyl compound is obtained. This hydroxymethyl derivative condenses with trimethylbenzene on a 3:1 mole ratio to yield 1,3,5-trimethyl-2,4,6,-tris(3',5'-di-*tert*-butyl-4'-hydroxybenzyl)benzene [1709-70-2], which is widely used in the stabilization of polypropylene, particularly polypropylene fibers (62).

A large number of hindered phenolic antioxidants are based on the Michael addition of 2,6-di-*tert*-butylphenol and methyl acrylate under basic catalysis to yield the hydrocinnamate which is a basic building block used in the production of octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate, [2082-79-3], tetrakis(methylene-3(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate)methane [6683-19-8], and many others (63,64). These hindered phenolic antioxidants are the most widely used primary stabilizers in the world and are used in polyolefins, synthetic and natural rubber, styrenics, vinyl polymers, and engineering resins. 2,6-Di-*tert*-butylphenol is converted to a methylene isocyanate which is trimerized to a triazine derivative 1,3,5-tris(3',5'-di-*tert*-butyl-4'-hydroxybenzyl)isocyanurate [27676-62-6]; this molecule has a special application in the protection of articles made from polypropylene fibers, such as surgical gowns, that are sterilized by ionizing radiation (65). Other uses for 2,6-di-*tert*-butylphenol include the production of a diisopropylidene sulfide derivative which is a cholesterol-lowering drug. 2,6-Di-*tert*-butylphenol is also used in the production of 4,4'-biphenol [92-88-6] which is used as a replacement for bisphenol-A in the production of liquid crystal polyesters, polysulfones, and polyetherimides. In these applications biphenol imparts an increased rigidity and higher heat distortion temperature to the polymer. Pure 2,6-di-*tert*-butylphenol is used as is as an antioxidant in oils and greases and the crude alkylate from the alkylation of phenol with isobutylene is commonly used in gasoline, diesel fuels, and jet fuels (66).

With the growth in thermoplastic materials replacing more traditional materials such as glass, wood, paper, and metal, the growth rate for 2,6-di-*tert*-butylphenol is estimated to be above average and could be significantly increased if the use of 4,4'-biphenol in production of high performance engineering plastics becomes a commercial success (see Table 3).

Di-sec-butylphenol (DSBP) is produced by the alkylation of phenol with 1-butene or 2-butene under acidic or aluminum catalysis. The production of di-*sec*-butylphenol under acid catalysis gives a 2 to 1 mixture of 2,4-di-*sec*-butylphenol and 2,6-di-*sec*-butylphenol [2,4-bis(1-methylpropyl)phenol and 2,6-bis(1-methylpropyl)phenol]. Under aluminum catalysis 2,6-di-*sec*-butylphenol is produced in greater than 90% yield. Di-*sec*-butylphenol [31291-60-8] is available in 55-gal drums (208-L) and in bulk shipments in tank wagons and railcars.

The only significant use for di-*sec*-butylphenol is a specialty nonionic surfactant produced by reaction with ethylene oxide under base catalysis. This surfactant is registered with EPA for use in emulsifying agrochemicals (see Table 3).

2,4-Dicumylphenol (2,4-DCP) or 2,4-bis(1-methyl-1-phenylethyl)phenol is produced by the alkylation of phenol with α -methylstyrene under acidic catalysis. The crude alkylation product contains 4-cumylphenol, 2,4-dicumylphenol, and 2,4,6-tricumylphenol along with some olefin oligomers. Pure 2,4-dicumylphenol can be obtained either by vacuum fractional distillation or crystallization from a suitable solvent. 2,4-Dicumylphenol [2772-45-4] is packaged in 55-gal drums (208-L) and sold as a bulk material in molten form.

The largest use for 2,4-dicumylphenol is in a production of a uv stabilizer of the benzotriazole class, 2-(2'-hydroxy-3',5'-dicumylphenyl)benzotriazole [70321-86-7] which is used in engineering thermoplastics where high molding temperatures are encountered (67). The high molecular weight of 2,4-dicumylphenol makes this uv stabilizer the highest molecular weight benzotriazole based uv stabilizer in commercial production (see Table 3).

2,6-Dimethylphenol (2,6-xlenol) is produced by the gas phase alkylation of phenol with methanol using modified alumina catalysis. The crude product contains 2-methylphenol, 2,6-dimethylphenol, a minor amount of 2,4-dimethylphenol, and a mixture of trimethylphenols. The 2,6-dimethylphenol is purified by fractional distillation. The mixture of di- and trimethylphenols is sold as cresylic acid for use as a solvent. 2,6-Dimethylphenol [576-26-1] is available in 55-gal drums (208-L) and in bulk shipments in tank wagons and railcars.

The oxidative coupling of 2,6-dimethylphenol to yield poly(phenylene oxide) represents 90–95% of the consumption of 2,6-dimethylphenol (68). The oxidation with air is catalyzed by a copper–amine complex. The poly(phenylene oxide) derived from 2,6-dimethylphenol is blended with other polymers, primarily high impact polystyrene, and the resulting alloy is widely used in housings for business machines, electronic equipment and in the manufacture of automobiles (see POLYETHERS, AROMATIC). A minor use of 2,6-dimethylphenol involves its oxidative coupling to 3,3',5,5'-tetramethyl-4,4'-biphenol [2417-40-1] (69). Tetramethylbiphenol is used as a monomer in the production of specialty polycarbonates and reacts with epichlorohydrin to produce an epoxy resin.

The worldwide consumption of 2,6-dimethylphenol is difficult to estimate accurately because the majority is captively consumed (see Table 3). Growth rate for 2,6-dimethylphenol is directly related to the growth of engineering resins, which is generally predicted to be above average.

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John F. Lorenc
Gregory Lambeth
William Scheffer
Schenectady Chemicals, Inc.

ALKYL PHOSPHATES.

See PHOSPHORIC ACIDS AND PHOSPHATES.

ALKYL SULFATES.

See SULFURIC ACID AND SULFUROUS ESTERS.

ALLANTOIN.

See URIC ACID.

ALLENE.

See HYDROCARBONS.

ALLEOCHEMICALS.

See GROWTH REGULATORS—PLANTS.

ALLERGENS.

See ANTI ASTHMATIC AGENTS; INDUSTRIAL HYGIENE AND PLANT SAFETY; TOXICOLOGY.

ALLITOL.

See SUGAR ALCOHOLS.

ALLOSE.

See CARBOHYDRATES; SUGAR.

ALLOYS.

See HIGH TEMPERATURE ALLOYS; SHAPE MEMORY ALLOYS; various elemental entries, eg, MANGANESE AND MANGANESE ALLOYS.

ALLULOSE.

See CARBOHYDRATES; SUGAR; SYRUPS.

ALLYL ALCOHOL AND MONOALLYL DERIVATIVES

Allyl alcohol, $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$ (2-propen-1-ol) [107-18-6] is the simplest unsaturated alcohol. One hydrogen atom can easily be abstracted from the allylic methylene ($-\text{CH}_2-$) to form a radical. Since the radical is stabilized by resonance with the $\text{C}=\text{C}$ double bond, it is very difficult to get high molecular weight polymers by radical polymerization. In spite of the fact that allyl alcohol has been produced commercially for some years (1), it has not found use as a monomer in large volumes as have other vinyl monomers.

More recently, however, the technology of introducing a new functional group to the double bond of allyl alcohol has been developed. Allyl alcohol is accordingly used as an intermediate compound for synthesizing raw materials such as epichlorohydrin and 1,4-butanediol, and this development is bringing about expansion of the range of uses of allyl alcohol.

Physical Properties

Allyl alcohol is a colorless liquid having a pungent odor; its vapor may cause severe irritation and injury to eyes, nose, throat, and lungs. It is also corrosive. Allyl alcohol is freely miscible with water and miscible with many polar organic solvents and aromatic hydrocarbons, but is not miscible with *n*-hexane. It forms an azeotropic mixture with water and a ternary azeotropic mixture with water and organic solvents (Table 1). Allyl alcohol has both bacterial and fungicidal effects. Properties of allyl alcohol are shown in Table 2.

Table 1. Azeotropic Boiling Points of Allyl Alcohol–Water–Organic Solvent Systems

Organic solvent	Boiling point, °C	Component, wt %		
		Allyl alcohol	Water	Solvent
none	88.9	72	28	
benzene	68.2	9.1	7.3	83.6
diallyl ether	77.8	8.7	12.4	78.9
allyl acetate	82.6	9	20	71
cyclohexane	66.2	10.9	8.1	81.0
toluene	80.6	31.4	15.2	53.4

Table 2. Properties of Allyl Alcohol^a

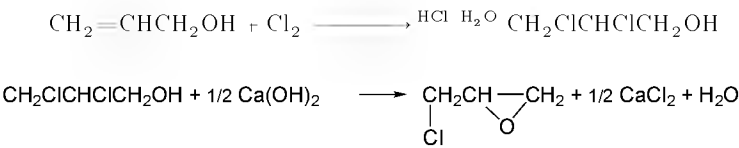
Property	Value
molecular formula	C ₃ H ₆ O
molecular weight	58.08
boiling point, °C	96.90
freezing point, °C	129.00
density, <i>d</i> ₄ ²⁰	0.8520
refractive index, <i>n</i> _D ²⁰	1.413
viscosity at 20°C, mPa·s(cP)	1.37
flash point ^b , °C	25
solubility in water at 20°C, wt %	infinity

^a Ref. 2.

^b Closed cup.

Chemical Properties

Addition Reactions. The C=C double bond of allyl alcohol undergoes addition reactions typical of olefinic double bonds. For example, when bromine is added, a good yield of 2,3-dibromopropanol is obtained although 1,2,3-tribromopropane is obtained as a by-product. 1,2,3-tribromopropane is formed from substitution of the hydroxyl group of allyl alcohol by bromide and further addition of bromine to the C=C double bond. When this addition reaction is carried out in 2,3-dibromopropanol solvent, the substitution reaction is reduced and the yield of 2,3-dibromo adduct is increased (3). The addition of chlorine is different from that of bromine; the yield of 2,3-dichloro adduct is low (4), and much intermolecularly condensed ether by-product is formed. When hydrogen chloride dissolved in a solvent, such as a low boiling point ether, is used, the yield of 2,3-dichloro adduct can be increased (5). Furthermore, when an aqueous solution of hydrogen chloride above 45 wt % is used, the formation of ether by-product can be reduced, as can the formation of chlorohydrin which normally occurs in aqueous chlorine solution. Thus, a high yield of 2,3-dichloropropanol [616-23-9] can be obtained. For example, when chlorination is done continuously in a 50–60 wt % aqueous solution of hydrogen chloride at 0°C, allyl alcohol reacts completely with chlorine and 2,3-dichloropropanol is obtained in 95% yield (6). Epichlorohydrin [106-89-8] is obtained by saponifying 2,3-dichloropropanol with calcium hydroxide.



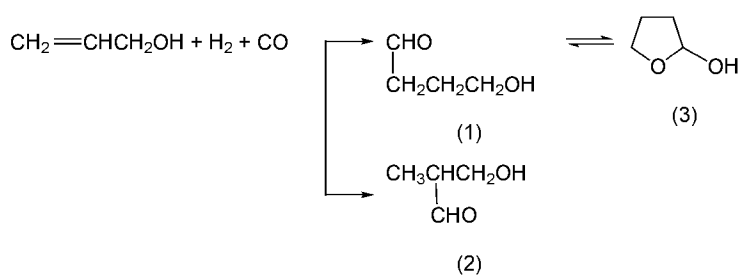
In fact, epichlorohydrin is being industrially manufactured by this method (7). The merit of this method is that it consumes only half the amount of chlorine and Ca(OH)₂ compared to that of the method via allyl chloride.

In the reaction of allyl alcohol with an aqueous chlorine solution, addition of hypochlorous acid to the double bond of allyl alcohol yields glycerol monochlorohydrin and as a by-product, glycerol dichlorohydrin. Thus, a poor yield of glycerol monochlorohydrin is obtained (8). To improve the yield of glycerol monochlorohydrin, addition of sodium carbonate in an amount equivalent to that of the hydrogen chloride in the aqueous chlorine solution, has been proposed (9).

When thiol is added to the double bond of allyl alcohol under radical forming conditions, Markovnikov reaction selectivity takes place. Mercury compounds, light, and oxygen accelerate the addition reaction. In the presence of (CH₃S)₂Hg, light, and oxygen, CH₃S(CH₂)₃OH can be obtained in 93% yield. In the presence of light and oxygen only, the yield decreases to 61%; the reaction cannot occur in the presence of light only (10). On the other hand, under ionic reaction conditions, an anti-Markovnikov reaction takes place (11).

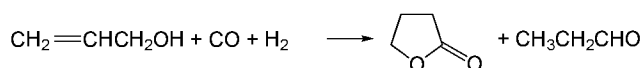
Under alkaline conditions, an amine addition reaction can occur. For example, in the reaction of C₆H₅CH₂CH₂NH₂ and allyl alcohol in the presence of sodium alcoholate at 108°C for 80 h, 43.4% *N*-(3-hydroxypropyl)phenylethylamine is formed (12).

Hydroformylation. Hydroformylation of allyl alcohol is a synthetic route for producing 1,4-butanediol [110-63-4], a raw material for poly(butylene terephthalate), an engineering plastic (qv); many studies on the process have been carried out.



After it was found that the rhodium carbonyl–triphenylphosphine–complex, $\text{HRh}(\text{CO})[\text{P}(\text{C}_6\text{H}_5)_3]_3$, is very effective in increasing the yield of hydroformylated product, many studies were done in greater detail with rhodium catalysts (13). The reactions are generally performed under the following conditions: 60–100°C, 0.69–3.4 MPa (7–35 kg cm²), H_2 to CO molar ratio more than one, and excess ligand phosphine. By-products are branched aldehyde (2), 2-hydroxymethylpropionaldehyde [38433-80-6], propionaldehyde produced by isomerization of allyl alcohol and *n*-propanol produced by hydrogenation of allyl alcohol. The types of by-products and the yield are affected by the reaction temperature, the molar ratio between phosphine and rhodium, the kind of phosphine, and the molar ratio between H_2 and CO. The yield of linear aldehyde (1), 4-hydroxybutyraldehyde [25714-71-0], depends on the kind of ligand. A yield of 60–70% is obtained even with excess triphenylphosphine, but a yield of more than 80% is obtained with 1-bis(diphenylphosphino)ferrocene (14). Addition of a great excess of triphenylphosphine causes a gradual decrease in catalytic activity. On the other hand, addition of excess triphenylphosphine and bidentate phosphine, especially, 1,4-bis(diphenylphosphino) butane to the rhodium complex in equimolar amounts enables the catalytic activity to be maintained, and the molar ratio of linear aldehyde to branched aldehyde is 9:1 and the selectivity to 2-hydroxytetrahydrofuran [5371-52-8] (3) is 80% (13). In the case of homogeneous reaction, separation and recovery of catalyst poses a problem. To solve this problem, gas-phase reaction was attempted and it was found that linear aldehyde is selectively produced in 99% yield, using silica containing a small amount of alumina as the catalyst carrier. From this experimental result, the gas-phase reaction was found to be regiospecific. Catalytic activity is maintained for at least 250 hours by using tris-*p*-tolylphosphine (15).

In the reaction of allyl alcohol with carbon monoxide using cobalt carbonyl, $\text{Co}(\text{CO})_8$ as the catalyst, in the presence of a small amount of hydrogen and carbon monoxide under pressure, 9.8 MPa (1420 psi), at 100°C, intramolecular hydroesterification takes place, yielding γ -butyrolactone [96-48-0] (16).

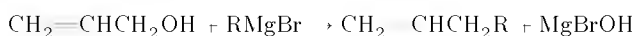


With solvents having a nitrile group like acetonitrile, the selectivity of γ -butyrolactone is increased, resulting in a yield of 60%.

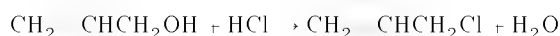
Substitution of Hydroxyl Group. The substitution activity of the hydroxyl group of allyl alcohol is lower than that of the chloride group of allyl chloride and the acetate group of allyl acetate. However, allyl alcohol undergoes substitution reactions under conditions in which saturated alcohols do not react. Reactions proceed in catalytic systems in which a π -allyl complex is considered as an intermediate. It can thus be said that this substitution reaction is a specific reaction of allyl alcohol. The reaction of allyl alcohol with diethylamine, using palladium acetyl acetonate [14024-61-4] and triphenylphosphine [603-35-0] as the catalyst, at 50°C for 30 min yields 95% diethylallylamine (17). However, in this reaction, the catalyst is deactivated gradually during the reaction due to oxidation of phosphine by allyl alcohol. The reactivity of ammonia is lower than that of dialkylamine and even under the above-mentioned conditions, a substitution reaction cannot take place. Catalytic activity decreases markedly in the presence of ammonia; however, using diphosphine as the ligand, improves catalytic activity and stability (18). For instance, in the reaction of allyl alcohol and ammonia with palladium acetyl acetonate and 1,3-bis(diphenylphosphono)propane [6737-42-4] as the catalyst and propylene glycol as the solvent at 110°C for 4 h, a mixture of monoallylamine, diallylamine, and triallylamine is obtained with a 73.5% conversion of allyl alcohol and a selectivity of 98.9% to amines. In the conventional process for synthesizing allylamine from allyl chloride and amine, the reaction vessel becomes badly corroded (19). Moreover, it has the disadvantage of forming sodium chloride as a by-product. The new process is, therefore, economically attractive.

With active methylene compounds, the carbanion substitutes for the hydroxyl group of allyl alcohol (17,20). Reaction of allyl alcohol with acetylacetone at 85°C for 3 h yields 70% monoallyl compound and 26% diallyl compound. Malonic acid ester in which the hydrogen atom of its active methylene is substituted by *N*-acetyl, undergoes the same substitution reaction with allyl alcohol and subsequently yields α -amino acid by decarboxylation (21).

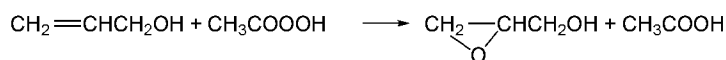
In the reaction of allyl alcohol and Grignard reagent with $[\text{P}(\text{C}_6\text{H}_5)_3]_2\text{-NiCl}_2$ as the catalyst, formation of the carbon–carbon bond proceeds at a high yield (22).



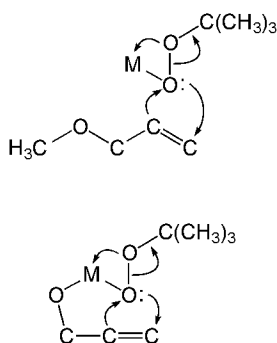
For reaction with hydrogen halides, the substitution reaction with halide ion easily occurs when a cuprous or cupric compound is used as the catalyst (23) and yields a halogenated allyl compound. With a cuprous compound as the catalyst at 18°C, the reaction is completed in 6 h. Zinc chloride is also a good catalyst (24), but a by-product, diallyl ether, is formed.



Oxidation. The $\text{C}=\text{C}$ double bond of allyl alcohol undergoes epoxidation by peroxide, yielding glycidol [556-52-5]. This epoxidation reaction is applied in manufacturing glycidol as an intermediate for industrial production of glycerol [56-8-5], using a typical epoxidation agent such as peracetic acid.



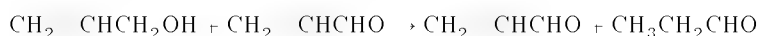
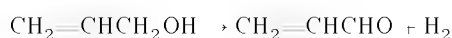
In the past, FMC Corporation industrially produced glycerol in two steps: production of glycidol from allyl alcohol in high boiling point ketone solvent, followed by hydrolysis of glycidol to glycerol. Daicel Chemical Industries produces glycerol with a reaction–distillation system to prevent a decrease in yield caused by intermolecular reaction of glycidol, by feeding water to the distillation column and converting the main part of the glycidol to glycerol *in situ* and not isolating glycidol as an intermediate (25). Shell Chemical Company produced glycerol, using hydrogen peroxide as the oxidant (25). The reaction, which is carried out with tungstic acid, H_2WO_4 , as the catalyst, enables glycerol to be obtained in one step. When the pH (4–6), concentration and other conditions are controlled and the reaction temperature is at 45°C, yield of glycidol can reach 82–87% (26). Degussa A.G. produced glycidol by using sodium tungstate, NaHWO_4 , as the catalyst. It is necessary to use a catalyst in the epoxidation reaction of olefinic double bonds (such as hydrogen peroxide or alkyl hydroperoxide). However, epoxidation of allyl alcohol is different from that of typical olefins in reactivity considerations such as the reaction rate and selectivity, because of interaction between the hydroxyl group of allyl alcohol and the catalyst. When tungstic acid is used as the catalyst, the reaction rate of epoxidation of allyl alcohol by hydroperoxide as the oxidation reagent is 30 times faster than that of allyl chloride (27). Further, in the case of epoxidation by $(\text{CH}_3)_3\text{COOH}$ with a vanadium catalyst, the epoxidation rate of allyl alcohol is 1000 times faster than that of methyl allyl ether. It is postulated that a covalent alkoxide intermediate is formed between the metal and the hydroxyl group (28).



This chemical bond between the metal and the hydroxyl group of allyl alcohol has an important effect on stereoselectivity. Asymmetric epoxidation is well-known. The most stereoselective catalyst is $\text{Ti}(\text{OR})_3$, which is one of the early transition metal compounds and has no oxo group (28). Epoxidation of isopropylvinylcarbinol [4798-45-2] (1-isopropylallyl alcohol) using a combined chiral catalyst of $\text{Ti}(\text{OR})_4$ and L-(+)-diethyl tartrate and $(\text{CH}_3)_3\text{COOH}$ as the oxidant, stops at 50% conversion, and the erythro:threo ratio of the product is 97:3. The reason for the reaction stopping at 50% conversion is that only one enantiomer can react and the unreacted enantiomer is recovered in optically pure form (28).

Allyl alcohol can be easily oxidized to yield acrolein [107-02-8] and acrylic acid [79-10-7]. In an aqueous potassium hydroxide solution of RuCl_3 , allyl alcohol is oxidized by a persulfate such as $\text{K}_2\text{S}_2\text{O}_8$ at room temperature, yielding acrylic acid in 45% yield (29). There are also examples of gas-phase oxidation reactions of allyl alcohol, such as that with Pd–Cu or Pd–Ag as the catalyst at 150–200°C, in which allyl alcohol is converted by 80% and acrolein and acrylic acid are selectively produced in 83% yield (30).

Miscellaneous Reactions. Allyl alcohol can be isomerized to propionaldehyde [123-38-6] in the presence of solid acid catalyst at 200–300°C. When copper or alumina is used as the catalyst, only propionaldehyde is obtained, because of intramolecular hydrogen transfer. On the other hand, acrolein and hydrogen are produced by a zinc oxide catalyst. In this case, it is considered that propionaldehyde is obtained mainly by intermolecular hydrogen transfer between allyl alcohol and acrolein (31).



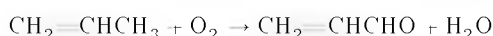
Friedel-Crafts reaction of allyl alcohol with benzene or alkylbenzene yields many kinds of products, in which the reaction species and the product ratio depend on the type of catalyst. Zinc chloride is the most effective catalyst for producing allyl compounds by this reaction (32).

Allyl alcohol undergoes reactions typical of saturated, aliphatic alcohols. Allyl compounds derived from allyl alcohol and used industrially, are widely manufactured by these reactions. For example, reactions of allyl alcohol with acid anhydrides, esters, and acid chlorides yield allyl esters, such as diallyl phthalates and allyl methacrylate; reaction with chloroformate yields carbonates, such as diethylene glycol bis(allyl carbonate); addition of allyl alcohol to epoxy groups yields products used to produce allyl glycidyl ether (33,34).

Industrial Manufacturing Processes for Allyl Alcohol

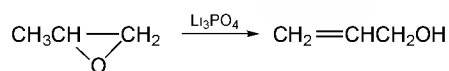
There are four processes for industrial production of allyl alcohol. One is alkaline hydrolysis of allyl chloride (1). In this process, the amount of allyl chloride, 20 wt % aqueous NaOH solution, water, and steam are controlled as they are added to the reactor and the hydrolysis is carried out at 150 °C, 1.4 MPa (203 psi) and pH 10–12. Under these conditions, conversion of allyl chloride is 97–98%, and allyl alcohol is selectively produced in 92–93% yield. The main by-products are diallyl ether and a small amount of high boiling point substance. The alkali concentration and pH value are important factors. At high alkali concentrations, the amount of by-product, diallyl ether, increases and at low concentrations, conversion of allyl chloride does not increase.

A second process has two steps. The first step is oxidation of propylene [115-07-1] to acrolein and the second step is reduction of acrolein to allyl alcohol by a hydrogen transfer reaction, using isopropyl alcohol (25).

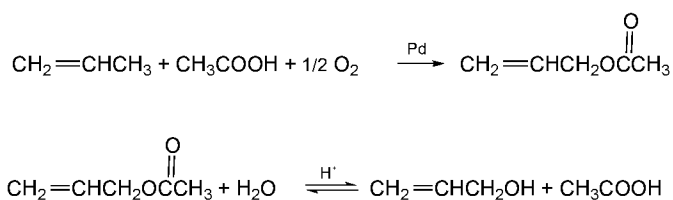


This process has defects such as co-production of acetone and a low yield of allyl alcohol.

At present, neither of these two processes are being used industrially. Another process is isomerization of propylene oxide [75-56-9].



In this process, the fine powder of lithium phosphate used as catalyst is dispersed, and propylene oxide is fed at 300°C to the reactor, and the product, allyl alcohol, together with unreacted propylene oxide is removed by distillation (25). By-products such as acetone and propionaldehyde, which are isomers of propylene oxide, are formed, but the conversion of propylene oxide is 40% and the selectivity to allyl alcohol reaches more than 90% (25). However, allyl alcohol obtained by this process contains approximately 0.6% of propanol. Until 1984, all allyl alcohol manufacturers were using this process. Since 1985 Showa Denko K.K. has produced allyl alcohol industrially by a new process which they developed (6,7). This process, which was developed partly for the purpose of producing epichlorohydrin via allyl alcohol as the intermediate, has the potential to be the main process for production of allyl alcohol. The reaction scheme is as follows:



In the first step of the reaction, the acetoxylation of propylene is carried out in the gas phase, using solid catalyst containing palladium as the main catalyst at 160–180°C and 0.49–0.98 MPa (70–140 psi). Components from the reactor are separated into liquid components and gas components. The liquid components containing the product, allyl acetate, are sent to the hydrolysis process. The gas components contain unreacted gases and CO_2 . After removal of CO_2 , the unreacted gases, are recycled to the reactor. In the second step, the hydrolysis, which is an equilibrium reaction of allyl acetate, an acid catalyst is used. To simplify the process, a solid acid catalyst such as ion-exchange resin is used, and the reaction is carried out at the fixed-bed liquid phase. The reaction takes place under the mild condition of 60–80°C and allyl alcohol is selectively produced in almost 100% yield. Acetic acid recovered from the

hydrolysis process, is reused in the first step. As a result, it can be said that allyl alcohol is produced from oxidation of propylene by oxygen. Allyl alcohol forms an azeotropic mixture with water, and the mixture is a homogeneous liquid. Therefore, to obtain dry allyl alcohol, ternary azeotropic distillation and dehydration are required. This process for allyl alcohol production is shown in Figure 1.

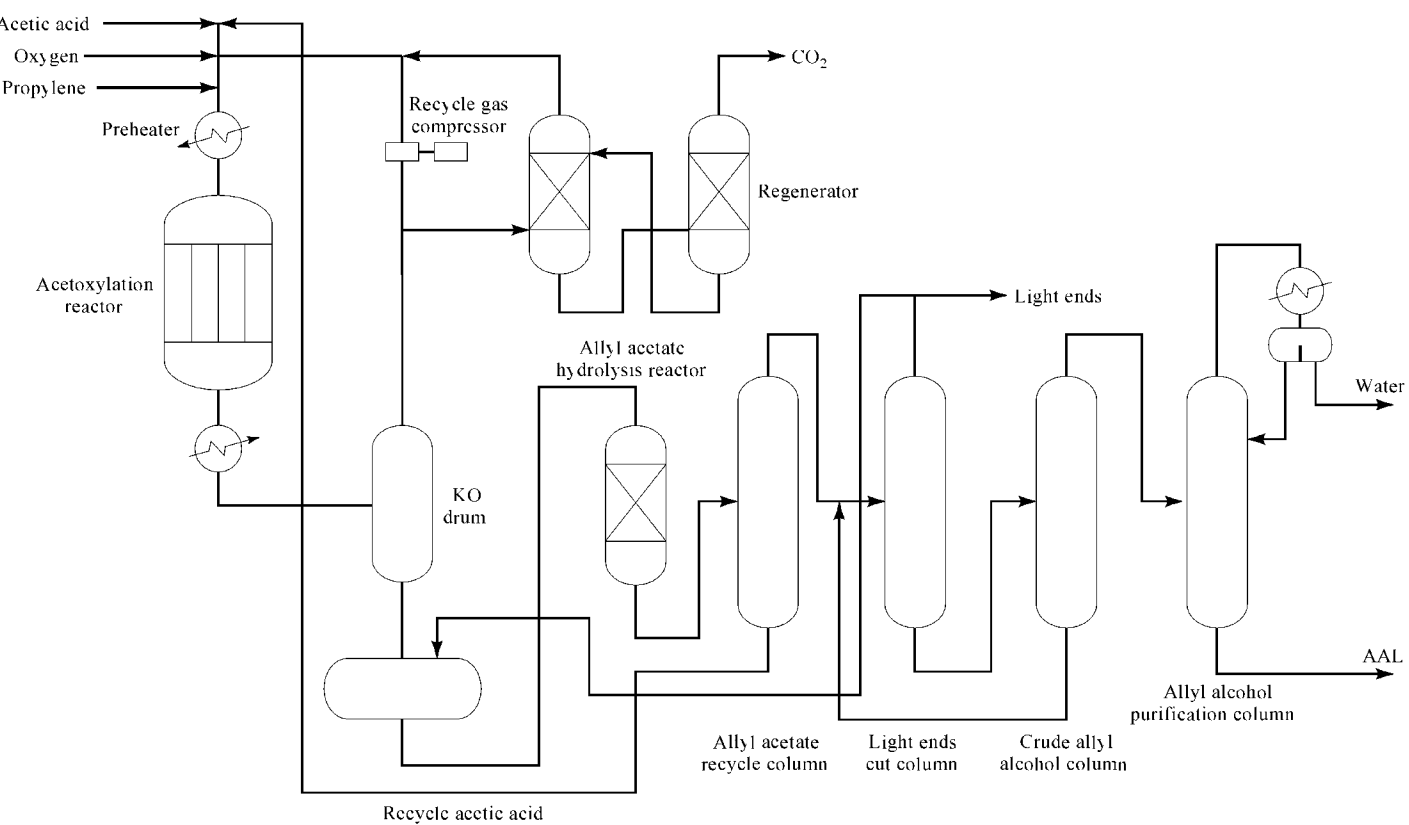


Fig. 1. The process for allyl alcohol (AAL) production via allyl acetate.

The world's manufacturers of allyl alcohol are ARCO Chemical Company, Showa Denko K.K., Daicel Chemical Industries, and Rhône-Poulenc Chimie; total production is approximately 70,000 tons per year.

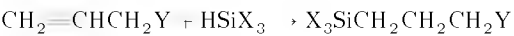
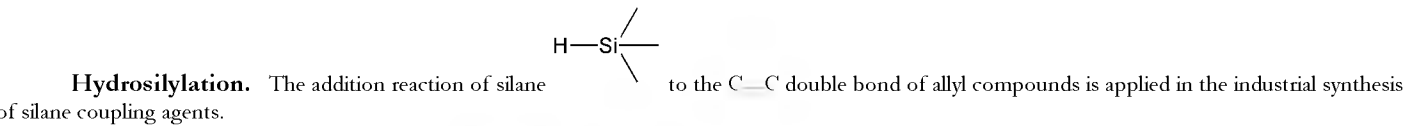
Uses of Allyl Alcohol

Recently, the uses of allyl alcohol have been greatly changing and increasing. Before 1985, the two principal uses of allyl alcohol were as a raw material for glycerol, which is industrially produced by the Daicel Chemical Company, and a monomer, diethylene glycol bis(allyl carbonate), for plastic optical lens (see ALLYL MONOMERS AND POLYMERS). It is estimated that each use is consuming several thousand tons of allyl alcohol per year. In 1985, Showa Denko K.K. started producing about 12,000 tons per year of epichlorohydrin using allyl alcohol as the raw material (7). Further in 1990, its production of epichlorohydrin increased to 24,000 tons per year, consuming 17,000–18,000 tons per year of allyl alcohol. Some epichlorohydrin manufacturers are planning to switch their production process to the allyl alcohol process. The consumption of allyl alcohol may therefore be expected to expand. In 1990, ARCO Chemical Company put on stream the world's largest allyl alcohol production plant, using the propylene oxide isomerization process, and at the same time, started producing 1,4-butanediol, consuming most of the allyl alcohol they produced, as the raw material. Since their production of 1,4-butanediol is said to be 35,000 tons per year, approximately 30,000 tons per year of allyl alcohol are needed. This is the first example of industrially producing 1,4-butanediol using allyl alcohol as the raw material (see ACETYLENE DERIVED CHEMICALS). With ARCO Chemical Company starting up the allyl alcohol production plant, FMC Corporation stopped their allyl alcohol production plant. In addition to these applications, allyl alcohol is used as the raw material for producing allyl esters (diallyl phthalates and allyl methacrylate), allyl ether (allyl glycidyl ether), and a styrene–allyl alcohol copolymer. The styrene–allyl alcohol copolymer is produced by Monsanto Chemical Company (35) and is used in water-soluble paints, alkyd resins (qv), and urethanes as polyols.

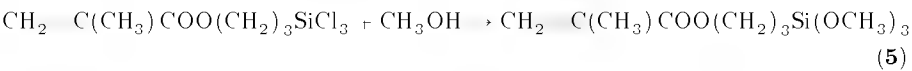
Monoallyl Derivatives

In this article, mainly monoallyl compounds are described. Diallyl and triallyl compounds used as monomers are covered in the article entitled [ALLYL MONOMERS AND POLYMERS](#) and also in the literature (36,37).

REACTIVITY OF ALLYL COMPOUNDS



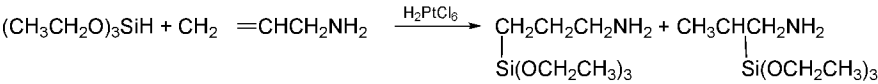
Usually, trichlorosilane, trialkoxysilane, methyl dichlorosilane, and methyl dialkoxysilane are used. For example, the reaction of trichlorosilane with allyl methacrylate is as follows:



Platinum compounds are the most active catalysts for hydrosilylation. Compounds such as H_2PtCl_4 and $\text{PtCl}_2(\text{CH}_3\text{CHCOCH}_3)_2$ are effective. In the reaction with allyl methacrylate, which has two C=C double bonds, the allylic double bond selectively reacts. For example, while refluxing 10.5 moles (1422

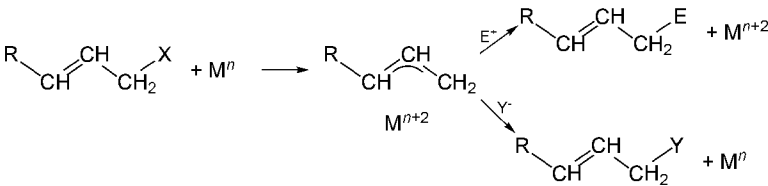
g) of HSiCl_3 with 1 mL of 0.01 M $\text{PtCl}_2(\text{CH}_3\text{COCHCOCH}_3)$ in an acetone solution, as the catalyst, allyl methacrylate is added dropwise over 2 h and the reaction solution is agitated for 2 h at room temperature, whereupon 9.94 moles (2600 g) of product (4) is obtained after removal of excess HSiCl_3 (38). Also, in the case of allyl glycidyl ether, the allylic double bond is more reactive than the glycidyl group to silane. In the presence of mesityl oxide dichloro platinum complex as the catalyst, trimethoxysilane reacts with allyl glycidyl ether of equivalent moles at 130–140°C yielding 91.5% (3-glycidioxypropyl)-trimethoxysilane [2530-83-8] (39).

These examples show that silane reacts selectively with the γ -position of allyl compounds. However, in its reaction with allyl amine, a side reaction in which silane binds to the β -position takes place (40).

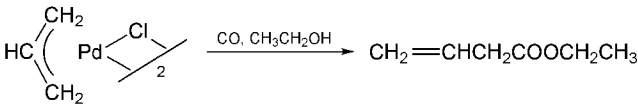


Use of $\text{HRh}(\text{CO})[\text{P}(\text{C}_6\text{H}_5)_3]_3$ as the catalyst and an excess of triphenylphosphine improves the $\gamma:\beta$ ratio. For example, reaction of triethoxysilane with allylamine of equivalent moles at 150°C for 10 h, yields the γ -form product in more than 70% and the $\gamma:\beta$ ratio is 26. Compared with this, when H_2PtCl_6 is used as the catalyst, the $\gamma:\beta$ ratio is 4 (41). Furthermore, when $\text{Rh}[(\mu\text{-P}(\text{C}_6\text{H}_5)_2\text{-}(\text{cyclooctadiene}))_2]$ is used as the catalyst, the yield of γ -form product is selectively increased to 92% and that of β -form product is decreased to 1.1% (42).

π -Allyl Complex Formation. Allyl halide, allyl ester, and other allyl compounds undergo oxidative addition reactions with low atomic valent metal complexes to form π -allyl complexes. This is a specific reaction of allyl compounds.



This π -allyl complex does not react with electrophilic reagent, E^+ , in a catalytic way because the central metal remains in an oxidized state even after reaction. On the other hand, in the reaction with nucleophilic reagent, Y^- , the central metal is easily reduced to M^n , and the oxidative addition of allyl compound with M^n again takes place. Thus, this reaction continues in a catalytic way. Allyl compounds that carry out oxidative addition have as their functional group, X, halogen, RCOO , ROCOO , $(\text{RO})_2\text{COO}$, RO , RNH , R_3N , NO_2 , RSO_2 , R_2S , and others. Metals that are effective as catalysts for the reaction of allyl compounds with nucleophilic reagents are Pd, Pt, Rh, Ru, Ni, Fe, Co, W, Mo, and others (43). Of these metals, Pd catalysts are the ones most studied. In the presence of nucleophilic reagent and carbon monoxide, a CO insertion can be done (44).



PHYSICAL PROPERTIES OF DERIVATIVES

The physical properties of some important monoallyl compounds are summarized in Table 3.

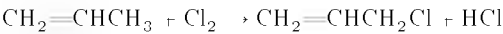
Table 3. Properties of Important Allyl Compounds

Property	Allyl chloride	Allyl acetate	Allyl methacrylate	Allyl glycidyl ether AGE ^a	Allyl amine	dimethylallylamine DMAA ^b
molecular formula	$\text{C}_3\text{H}_5\text{Cl}$	$\text{C}_5\text{H}_8\text{O}_2$	$\text{C}_7\text{H}_{10}\text{O}_2$	$\text{C}_5\text{H}_{10}\text{O}_2$	$\text{C}_3\text{H}_7\text{N}$	$\text{C}_5\text{H}_{11}\text{N}$
CAS Registry Number	[107-05-1]	[591-87-7]	[96-05-9]	[106-92-3]	[107-11-9]	[2155-94-4]
molecular weight	76.53	100.12	126.16	114.14	57.10	85.15
boiling point, °C	44.69	104	150	153.9	52.9	64.5
freezing point, °C	134.5	96	60	100	88.2	
density, d_4^{20}	0.9382	0.9276	0.934	0.9698	0.7627	0.72
refractive index, n_D^{20}	1.416	1.404	1.436	1.435	1.420	
viscosity at 20°C, mPa·s(cP)	3.36	0.52	13	1.20		0.44
flash point, °C	31.7	6	33	57.2	29	23
solubility in water at 20°C, %	0.36	2.8			infinity	
limits of inflammability, %	2.9	2.1			2.2	
	11.30	13.0			22	

^a Allyl glycidyl ether.
^b Dimethylallylamine.

ALLYL CHLORIDE

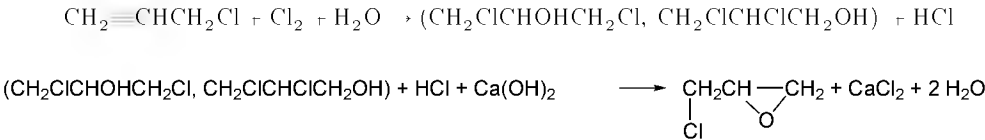
This derivative, abbreviated AC, is a transparent, mobile, and irritative liquid. It can be easily synthesized from allyl alcohol and hydrogen chloride (23). However, it is industrially produced by chlorination of propylene at high temperature.



The process involving allyl alcohol has not been industrially adopted because of the high production cost of this alcohol. However, if the allyl alcohol production cost can be markedly reduced, and also if the evaluated cost of hydrogen chloride, which is obtained as a by-product from the substitutive chlorination reaction, is cheap, then this process would have commercial potential. The high temperature propylene–chlorination process was started by Shell Chemical Corporation in 1945 as an industrial process (1). The reaction conditions are a temperature of 500°C, residence time 2–3 s, pressure 1.5 MPa (218 psi), and an excess of propylene to chlorine. The yield of allyl chloride is 75–80% and the main by-product is dichloropropane, which is obtained as a result of addition of chlorine. Other by-products include monochloropropenes, dichloropropenes, 1,5-hexadiene. At low temperatures, the amount of

by-product dichloropropane increases and above 550°C, the amount of by-product benzene increases. Excess propylene is recovered and recycled to the reactor after washing and dehydration treatment, and hydrogen chloride, the by-product is recovered as concentrated hydrochloric acid (1). The purity of allyl chloride in the market is 99–99.5°; the main impurities are 1,5-hexadiene and monochlorinated compounds.

Uses. Allyl chloride is industrially the most important allyl compound among all the allyl compounds (see CHLOROCARBONS AND CHLOROHYDROCARBONS, ALLYL CHLORIDE). It is used mostly as an intermediate compound for producing epichlorohydrin, which is consumed as a raw material for epoxy resins (qv). World production of AC is approximately 700,000 tons per year, the same as that of epichlorohydrin. Epichlorohydrin is produced in two steps: reaction of AC with an aqueous chlorine solution to yield dichloropropanol (mixture of 1,3-dichloropropanol and 2,3-dichloropropanol) by chlorohydrination, and then saponification with a calcium hydroxide slurry to yield epichlorohydrin.



In the second step, a distillation-reaction system is applied to prevent hydrolysis of epichlorohydrin, by removing epichlorohydrin and water as an azeotropic mixture from the top of the distillation column. This operation is known as steam-stripping. In addition to being used in the synthesis of epichlorohydrin, AC is also used as a raw material for synthesizing other allyl compounds such as allyl esters, allyl ethers, and allylamines by nucleophilic substitution, utilizing the easily substituting property of its chloride group.

ALLYL ESTERS

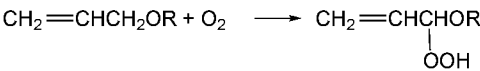
Allyl Acetate. Industrial production of allyl acetate started only rather recently. Nevertheless, among the allyl compounds, its production is second to that of allyl chloride. It is produced mostly for manufacturing allyl alcohol and its manufacture by acetoxylation of propylene has been described previously. The allyl acetate obtained may be separated and purified by distillation.

Allyl Methacrylate. At present, allyl methacrylate, AMA, is used mostly as a raw material for silane coupling agents. Utilizing the difference in the polymerizing ability of the allyl double bond and that of the methacrylate double bond, polymerization at the methacrylate double bond only is done by an anionic initiated reaction (45), yielding linear and soluble polymers with an allylic group attached to the pendant side chain. There are various methods for synthesizing AMA. For example, transesterification between allyl acetate and methyl methacrylate (46), esterification of methacrylic acid [79-41-4] with an excess of allyl alcohol (47), transesterification between methyl methacrylate [80-62-6] and allyl alcohol (48). This last method gives the highest yield of AMA. With an excess of methyl methacrylate and a combined catalyst of CaO and LiCl, allyl alcohol is converted by 97.7° and AMA is selectively produced in 95° yield (see also METHACRYLIC ACID AND DERIVATIVES).

Other monoallyl esters are esters of caproic acid and amyl glycolic acid, which are used as perfumes.

ALLYL ETHERS

The C—H bond of the allyl position easily undergoes radical fission, especially in the case of allyl ethers, reacting with the oxygen in the air to form peroxide compounds.



Therefore, in order to keep allyl ether for a long time, it must be stored in an air-tight container under nitrogen. Utilizing the peroxidation property, allyl glycidyl ether, glycerol monoallyl ether [25136-53-2], ethylene glycol monoallyl ether [111-45-45], and others are employed in unsaturated polyesters for "air-drying" coatings, but in this application, usually polyfunctional allyl ethers are used (36).

Allyl Glycidyl Ether. This ether is used mainly as a raw material for silane coupling agents and epichlorohydrin rubber. Epichlorohydrin rubber is synthesized by polymerizing the epoxy group of epichlorohydrin, ethylene oxide, propylene oxide, and allyl glycidyl ether, AGE, with an aluminum alkyl catalyst (36). This rubber has high cold-resistance.

In the synthesis of AGE with an acid as the catalyst, allyl alcohol is added to the epoxy group of epichlorohydrin, yielding 3-allyloxy-1-chloro-2-propanol [4638-03-3], which then undergoes cyclization with alkali to yield AGE. Catalysts such as H₂SO₄, SnCl₄, BF₃·4 (C₂H₅)₂O (33), heteropolyacids, HClO₄, and *p*-CH₃C₆H₄SO₃H (34) are used.

ALLYL AMINES

Allylamine. This amine can be synthesized by reaction of allyl chloride with ammonia at the comparatively high temperature of 50–100°C (49), or at lower temperatures using CuCl₂ (50) or CuCl (51) as the catalyst. In all such methods, a mixture of monoallyl, diallyl, and triallyl amines is obtained. For selectively obtaining monoallylamine, AAm, hydrolysis of by hydrochloric acid is used (52). The degree of polymerization of monoAAm is low. However, its hydrogen chloride salt is polymerized readily (53) and an industrial process for manufacturing polyAAm has been developed (54). AAm polymers are used as fixing agents for reactive dyes on fibers. If the production of silane coupling agents from monoAAm is established, industrial consumption of monoAAm may increase.

Organotin compounds derived from diallylamine and alkylthiophosphine, have low phytotoxicity and are useful as relatively stable insecticides (55).

Dimethylallylamine. When 1-dimethylamino-2,3-dichloropropane [5443-48-1], which is obtained by addition of chlorine to dimethylallylamine, DMAA, reacts with NaSCN, the dimethylamino group is transferred, yielding 1,3-dithiocyano-2-dimethylaminopropane, which is used to synthesize the carbamothioic ester, (CH₃)₂NCH(CH₂SCONH₂)₂ [15263-53-3] for pesticide use (56). Similarly, when 1-dimethylamino-2,3-dichloropropane reacts with Na₂S₂, 1,3-trithia-2-dimethylaminocyclopropane [31895-21-3], which is used as an insecticide (57), is produced. Furthermore, diallyldimethylammonium chloride (DADMAC) [7398-69-8], which is used as a monomer for synthesizing water-soluble polymers, is obtained from the reaction between DMAA and allyl chloride. DMAA is obtained in 95° yield by reaction of allyl chloride with two equivalent moles of dimethylamine at 23°C (58).

Safety and Handling

Most allyl compounds are toxic and many are irritants. Those with a low boiling point are lachrymators. Precautions should be taken at all times to ensure safe handling (59). Allyl compounds are harmful and may be fatal if inhaled, swallowed, or absorbed through skin. They are destructive to the tissues of the mucous membranes and upper respiratory tract, eyes, and skin (Table 4).

Table 4. Toxicity of Important Monoallyl Compounds^a

Compound	LD ₅₀ rat, mg/kg
allyl alcohol	64
allyl chloride	64

allyl acetate	130
allyl methacrylate	430
allyl glycidyl ether	922
allylamine	102

^a Ref. 59.

Handling and Storage. Workers should be provided with appropriate respirators (NIOSH MSHA approved), chemical resistant gloves, safety goggles, and other protective equipment. Work areas should be well-ventilated and be equipped with a safety shower and an eye bath. Care must be taken not to inhale any vapor and prevent it from getting into eyes, on skin, or on clothing. Prolonged or repeated exposure should be avoided. Thorough washing is required after handling. The compounds should be kept in a tightly closed container away from heat, sparks, and open flames and be stored in a cool dry place. Allyl ethers must be stored under nitrogen, but allyl (meth)acrylate must not be stored under an inert atmosphere in order to inhibit polymerization.

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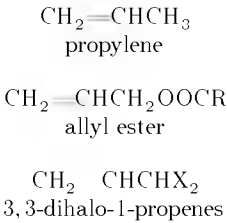
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ALLYL MONOMERS AND POLYMERS

Allyl compounds comprise a large group of ethylenic compounds having unique reactivities and uses often contrasting with those of typical vinyl-type compounds (styrenes, acrylics, vinyl esters and ethers, and related compounds). In allyl compounds the double bond is not substituted by a strong activating group to promote polymerization but is attached to a carbon which generally bears one or more reactive hydrogen atoms, eg,

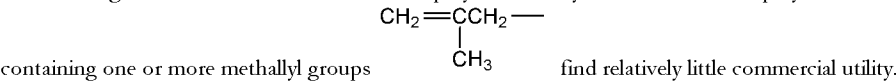


The allylic 1-alkenes, which yield useful polymers by Ziegler-type catalysts, are not discussed here. Unlike monovinyl compounds, monoallyl compounds do not form homopolymers of high molecular weight by free-radical or conventional ionic mechanisms; in general, only viscous liquid homopolymers of limited use have been obtained. This is explained by the low reactivity of the ethylenic double bond together with the high reactivity of hydrogen atoms on the allylic carbon in reducing the molecular weight by degradative chain transfer (1). However, numerous monoallyl compounds, including some that occur in nature, are known outside the polymer field. Examples are allyl sulfur compounds of onions, mustard, and other food flavors; allyl esters used in perfumes; allylic drugs and other compounds of biologic activity; as well as important intermediates for organic syntheses (see ALLYL ALCOHOL AND DERIVATIVES).

In contrast, many allyl compounds containing two or more reactive double bonds yield solid, high molecular weight polymers by initiation with suitable free-radical catalysts. A number of polyfunctional allyl esters have achieved importance in polymerization and copolymerization especially to obtain heat-resistant cast sheets and thermoset moldings. The reactivities of these monomers often permit polymerization in two stages: a solid prepolymer containing reactive double bonds can be molded by heating; then completion of polymerization gives cross-linked articles of superior heat resistance. The most important examples of allyl polymers are the CR-39 or diallyl diglycol carbonate polymers and molding materials based on diallyl phthalates.

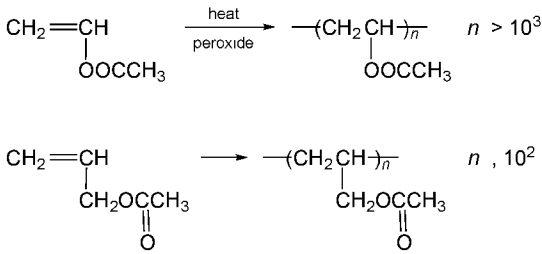
Another use is of minor proportions of polyfunctional allyl esters, eg, diallyl maleate, triallyl cyanurate, and triallyl isocyanurate, for cross-linking or curing preformed vinyl-type polymers such as polyethylene and vinyl chloride copolymers. These reactions are examples of graft copolymerization in which specific added peroxides or high energy radiation achieve optimum cross-linking (see COPOLYMERS).

Small proportions of mono- or polyfunctional allylic monomers also may be added as regulators or modifiers of vinyl polymerization for controlling molecular weight and polymer properties. Polyfunctional allylic compounds of high boiling point and compatibility are employed as stabilizers against oxidative degradation and heat discoloration of polymers. Diallyl ammonium salt copolymers are used in water purification and flocculation. Compounds

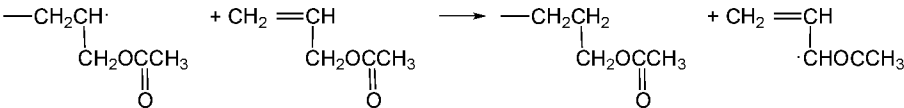


Reactivity of Allyl Compounds

Whereas vinyl acetate [108-05-4] (C₄H₈O₂), upon heating with benzoyl peroxide or other free-radical initiators, forms solid polymers of high molecular weight, similar treatment of allyl acetate [591-87-7] (C₅H₈O₂) gives only viscous liquid polymers.



This is explained by the low reactivity of the double bond of the allyl compound together with prevalence of chain termination through reaction of allylic H atoms as shown (2).



When vinyl and allyl monomers undergo chain transfer with solvents, so-called telomers may form, generally of rather low molecular weight (1). Because of the low reactivity and tendency to undergo chain transfer, small additions of most allyl compounds retard polymerization of typical vinyl monomers in free-radical systems (1,3) and may be useful in controlling molecular weight and structure in polymers. Many polyallyl compounds, upon heating with radical initiators, form solid high polymers in spite of chain transfer and loss of some double bonds by cyclization. With diallyl esters, such as diallyl phthalates, these slower polymerizations can be controlled more readily than in the polymerization of poly-functional vinyl compounds to give soluble prepolymers containing reactive double bonds (1,4). Cyclization in polymerization of diallyl compounds also can occur depending on the reaction conditions (5). In general, more cyclization occurs at lower monomer concentrations in solution and cross-linking is thereby reduced. Few allyl monomers have been polymerized to useful, well-characterized products of high molecular weight by ionic methods, eg, by Lewis acid or base catalysts. Polymerization of the 1-alkenes by Ziegler catalysts is an exception. However, addition of acidic substances, at room temperature or upon heating, often gives viscous liquid low mol wt polymers, frequently along with by-products of uncertain structure. In special cases allyl compounds, such as diallyl [592-42-7], (C₄H₁₀), (1,5-hexadiene) and diallyl ether [557-40-4] (C₄H₁₀O), can form high polymers

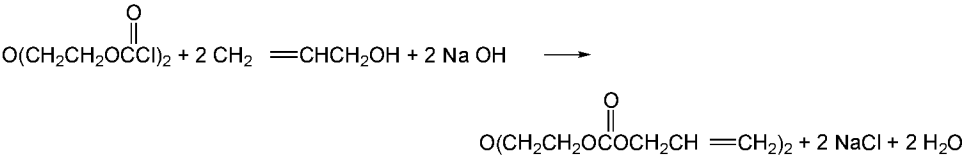
by addition of active hydrogen atoms. The best known case is the polymerization of diallyl with dimercaptans using free-radical initiation (6). These reactions are related to chain transfer and what has been called telocopolymerization (1,7).

Allyl compounds, depending on the structure of substituents, can undergo other reactions such as rearrangements, hydrolysis, and additions. Such reactions that may affect polymerization and have health considerations have been closely studied only with important industrial compounds (1).

Diallyl Carbonate Cast Plastics

From a number of diallyl esters investigated, diallyl diglycol carbonate or diethylene glycol bis(allyl carbonate), DADC, was developed to produce by bulk polymerization cast sheets, lenses, and other shapes of outstanding scratch resistance, and optical and mechanical properties. CR-39, a trademark of PPG Industries, is used to describe this material. DADC is the CR-39 monomer [142-22-3] from which CR-39 homopolymer [25656-90-0] (C₁₂H₁₈O₇)_x is made. CR-39 polymers have greater impact resistance and lower density than glass. These polymers are the most important clear, organic optical materials shaped by the casting process and by machining. Many polyfunctional ethylenic monomers have been patented (8,9).

DADC Monomers. Reaction of allyl alcohol in the presence of alkali with diethylene glycol bis(chloroformate), obtained from the glycol and phosgene, gives the monomer



In another method, phosgene is gradually passed into 1,2-propylene glycol (9). The chloroformate is washed, dried, and distilled at 266 Pa (2 mm Hg) and added slowly to a mixture of allyl alcohol and pyridine below 15°C. The purified monomer 1,2-propylene glycol bis(allyl carbonate) (C₁₁H₁ O) heated with lauroyl peroxide at 70°C gives a hard clear, polymer.

Reaction of allyl chloroformate and diethylene glycol in the presence of alkali with cooling is another method of preparing the diallyl carbonate ester DADC. The properties of diallyl carbonate monomers are given in Table 1.

Table 1. Properties of Diallyl Glycol Carbonate Monomers

Monomer	Molecular formula	CAS Registry Number	Boiling point, °C _{Ta} ^a	<i>n</i> _D ²⁰	<i>d</i> ₄ ²⁰
ethylene glycol bis(allyl carbonate)	C ₁₀ H ₁₄ O	[4074-91-3]	122 ₁₃₃	1.444	1.114
diethylene glycol bis(allyl carbonate) ^b	C ₁₂ H ₁₈ O ₇	[142-22-3]	160 ₂	1.452	1.143
triethylene glycol bis(allyl carbonate)	C ₁₄ H ₂₂ O ₈		polymerized	1.452	1.135
tetraethylene glycol bis(allyl carbonate)	C ₁ H ₂ O ₉			1.454	1.133
glycerol tris(allyl carbonate)	C ₁₅ H ₂₀ O ₉			1.456	1.194
ethylene glycol bis(methallyl carbonate)	C ₁₂ H ₁₈ O	[64653-60-7]	142 ₂	1.449	1.110

^a To convert Pa to mm Hg, multiply by 0.0075.

^b DADC (CR-39 monomer).

DADC monomer is a colorless liquid of mild odor and a viscosity of 9 mPas(cP) at 25°C. It is low in toxicity, but can produce skin irritation. It is fairly resistant to saponification by dilute alkali. Contact with strong alkali at higher temperature produces the more toxic allyl alcohol. Properties are given in Table 2 and the trade literature (10). DADC is soluble in common organic solvents and in methyl methacrylate, styrene, and vinyl acetate. It is partially soluble in amyl alcohol, gasoline, and ligroin. It is insoluble in ethylene glycol, glycerol, and water.

Table 2. Typical Properties of Commercial DADC Monomer^a

Property	Value
appearance	clear, colorless liquid
color, APHA	10
odor	none to slight
specific gravity	1.15 ²⁰ ₄
refractive index, <i>n</i> _D ²⁰	1.452
boiling point at 266 Pa ^b , °C	166
melting point (supercooled), °C	4 to 0
viscosity at 25°C, mm ² s (cSt)	15
flash point	
Seta closed cup, °C	173
Cleveland open cup, °C	186
water content, slightly hygroscopic, °o	0.1

^a Ref. 10.

^b To convert Pa to mm Hg, multiply by 0.0075.

The DADC monomer is available from several manufacturers, such as PPG Industries (CR-39), Akzo (Nouryset 200), Enichem (RAV) Rhone-Poulenc (XR-80), Tokuyama Soda (TS-16), and Mitsui Toatsu (MR-3).

DADC Homopolymerization. Bulk polymerization of CR-39 monomer gives clear, colorless, abrasion-resistant polymer castings that offer advantages over glass and acrylic plastics in optical applications. Free-radical initiators are required for thermal or photochemical polymerization.

Relatively high concentrations of organic peroxide or azo initiators are needed to obtain complete polymerization. After the reaction peak exotherm, polymerization slows down. Initiator concentrations must be high enough to complete conversion. Polymerization is inhibited by oxygen and copper, lead, and sulfur compounds (11).

Bulk polymerization has been studied at relatively low temperatures and in toluene and carbon tetrachloride solutions carried to low conversions (12). The effects of temperature and different organic peroxide initiators have been observed. The molecular weight of soluble polymer after 3° o conversion is ca *M*_n 19,000 and is somewhat dependent on initiator concentration or temperature between 35 and 65°C. With di-2-methylpentanoyl

peroxide, polymerization can be carried out at temperatures as low as 13°C. Nuclear magnetic resonance studies of the unsaturated prepolymer show that less than 10% of monomer units undergo cyclopolymerization.

Casting of DADC. Sheets, rods, and lens preforms are cast from CR-39 or prepolymer syrup by methods similar to those used for methacrylate ester syrups (13). Casting in glass cells with flexible gaskets is described in reference 4. Horizontal cells may be heated at 60–70°C to reach the gel state, and later at 125°C for completing the polymerization of thin sheets. In some cases polymerization of gel shapes can be completed by heating the outside of the mold with additional shaping. Shrinkage between monomer and polymer is about 14%. Under controlled casting conditions, density increases and initiator concentration decreases, as shown in Figure 1.

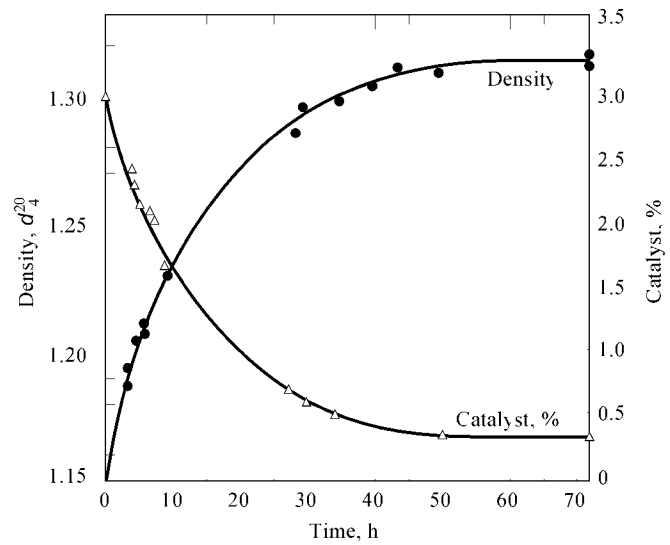


Fig. 1. Bulk polymerization of diethylene glycol bis(allylcarbonate) at 45°C with initial addition of 3.0% diisopropyl percarbonate. Rates of polymerization as measured by density and catalyst consumption decrease with time at a given temperature (14).

Many proprietary methods have been developed for casting and shaping DADC, especially for lenses. In one method DADC containing 3.5% diisopropyl percarbonate is prepolymerized by warming to a syrup of viscosity 40–60 mm² s (cSt) (15). Polymerization is continued in a lens for 18 h at 90°C followed by annealing at 120°C.

Scratch resistance of polymer from DADC is improved by novel mixtures of peroxide initiators such as 5% isopropyl percarbonate with 3.5% benzoyl peroxide (16). In order to force completion of polymerization and attain the best scratch resistance in lenses, uv radiation is applied (17). Eyeglass lenses can be made by prepolymerization in molds followed by removal for final thermal cross-linking (18).

Initially, DADC polymers were used in military aircraft for windows of fuel and deicer-fluid gauges and in glass-fiber laminates for wing reinforcements of B-17 bombers. Usage in impact-resistant, lightweight eyewear lenses has grown rapidly and is now the principal application. Other uses include safety shields, filters for photographic and electronic equipment, transparent enclosures, equipment for office, laboratory, and hospital use, and for detection of nuclear radiation.

Many lens casters use the term hard-resin lenses for DADC products; companies and trade names include American Optical (Aolite), Coburn (Supremacy I), Optical Radiation (Orcolite), and Silor Optical (Orma 1000). Additional information can be obtained from the Optical Manufacturers' Association, Falls Church, Va. Cast sheets of homopolymer and copolymers are supplied by the SGL Homalite Company, Foster Grant, and others. Welcast Plastics Company produces sheet castings for covers for welding-mask lenses. These covers for welding-mask lenses. These covers are resistant to hot metal fragments.

Typical properties of homopolymers from DADC are given in Tables 3 and 4, and in manufacturers' literature (20).

Table 3. Optical and Electrical Properties of DADC Homopolymer^{a, b}

Property	Value	ASTM method
refractive index at 20°C		
589.3 nm, n_D	1.4980	D542
dispersion factor f	0.0084	
Abbe number	59.3	
uv transmission ^c , %		
280 nm	6	
300 nm	27	
340 nm	78	
380 nm	88	
visible transmission ^c , %		
400–700 nm	89–91	
volume resistivity, $M\Omega\text{cm}$	10.4×10^{14}	D257
dielectric strength, V μm	13.9	D149
dielectric constant		
10 ³ Hz	4.2	D150
10 Hz	3.6	D150

^a Ref. 19.
^b CAS Registry Number [25656-90-0].
^c 2.7-mm thickness.

Table 4. Physical and Mechanical Properties of DADC Homopolymer^{a, b}

Property	Value	ASTM method
----------	-------	-------------

density at 20°C, g cm ³	1.31	D792
tensile strength, MPa ^c	35–41	D638
flexural yield strength, MPa ^c	52–58.6	D790
compressive strength, MPa ^c	155	D695
Izod impact, notched 25°C, J m ^d	10.7–21.4	D256
hardness		
Barcol, 15 s	25–28	
abrasion		
Taber (X PMMA) ^e	15–20	D1044
thermal conductivity, W (m·K)	0.21	C177
specific heat, kJ (kg·K) ^f	2.3	C351
linear coefficient of expansion °C		
40 to 25°C	8.1 × 10 ⁻⁵	D696
25 to 75°C	11.4 × 10 ⁻⁵	D696
75 to 125°C	14.3 × 10 ⁻⁵	D696
heat distortion at 1.8 MPa ^c , °C 10 mL	55–65	D648
glass transition, °C	85	
burn rate, 1.3–2.9-mm thickness, mm min	0.04	D635

^a Ref. 19.

^b CAS Registry Number [25656-90-0].

^c To convert MPa to psi, multiply by 145.

^d To convert J m to ftlb in., divide by 53.38.

^e Reference of poly(methyl methacrylate) 1.

^f To convert J to cal, divide by 4.184.

Coatings. In recent years methods have been developed to improve abrasion resistance of DADC polymer surfaces in optical devices and glazings by means of special coatings. Hard or glasslike coatings may be applied by near-vacuum vapor deposition of quartz (silica) or by hydrolysis of alkoxysilanes. Vapor deposition or sputtering processes of SiO₂ may be facilitated by electron beams or glow discharge. A second class of coatings are elastomeric polymers, which appear to be scratch-resistant because they heal by slow flow into the scratch depression. According to the Bayer abrader test, some coated DADC lenses are 10 times more resistant than the unmodified homopolymer surfaces. Subcoats and pretreatments of cast polymer surfaces have been patented. Antireflection, antistatic, and antifogging properties may also be improved by such coatings. Photochromic agents and color tints may be incorporated or added in coatings. A photochromic lens called Transitions has been announced by PPG (21). The lenses are designed to surface and edge in the same manner as lenses made from CR-39 under normal processing procedures. Many features such as blue color, uv absorption, and a scratch-resistant coating are inherent in the Transitions (trademark of PPG Industries) lenses (see CHROMOGENIC MATERIALS, PHOTOCHROMIC).

Modified Polymers and Copolymers. DADC pure monomer and mixtures with small amounts of comonomers or other additions are commercially available for casting. Monomer formulations are available including agents for protecting the eyes against uv light. Another grade is designed to absorb infrared radiation, and several modified monomers give copolymers of increased heat resistance and hardness. Heat-resistant castings have special advantages in high temperature vacuum deposition of scratch-resistant and antireflective coatings and metallization.

DADC may be polymerized industrially with small amounts of other miscible liquid monomers. Some acrylic ester monomers and maleic anhydride may accelerate polymerization. Copolymerization with methacrylates, diallyl phthalates, triallyl isocyanurate, maleates, maleimides, and unsaturated polyesters are among the examples in the early literature. Copolymers of DADC with poly-functional unsaturated esters give castings of high clarity for eyeglass lenses and other optical applications (20).

Various methacrylate esters have been disclosed as modifiers of DADC. Thus methyl methacrylate polymer may be dissolved in DADC and the sheets cast (22). When DADC is copolymerized with methyl methacrylate, a silane derivative may be added to control the release from the mold (23). CR-39 has been copolymerized with benzyl methacrylate and triallyl cyanurate, also with benzyl methacrylate [2495-37-6] and diallyl phthalate (24), and with trifluoroethyl methacrylate by a two-step process (25).

The DADC monomer has been copolymerized with small amounts of polyfunctional methacrylic or acrylic monomers. For example, 3° triethylene glycol dimethacrylate was used as a flexibilizing, cross-linking agent with a percarbonate as initiator (26). CR-39 and diethylene glycol diacrylate containing isopropyl percarbonate were irradiated with a mercury lamp to a 92% conversion and then cured at 150°C (27). By a similar two-step process DADC was copolymerized with methyl methacrylate and tetraethylene glycol dimethacrylate (28).

Light-focusing plastic rods and other optical devices with graduated refractive indexes may use DADC and other monomers (29). Preparation and properties of plastic lenses from CR-39 are reviewed in reference 30.

Polymeric Nuclear-Track Detectors. DADC polymer is used in solid-state track detectors (SSTD) of nuclear particles, including alpha-particles, fast neutrons, cosmic rays, and ions of elements of atomic number 10 and above. The outstanding sensitivity of the cast polymers in thin sheets and films to diverse types of ionic radiations with a wide range of mass-to-charge ratio has increased applications in nuclear and space sciences, medicine, mining, and ecological research (1). The tracks formed in the polymer are made visible by partial saponification of the polymer with warm aqueous alkali. The resulting surface holes or spots are counted under a light microscope or a scanning device. Polymerization has been optimized to improve sensitivity, resolution, and measurement. Electrons, x rays, and gamma rays are not recorded, but ions of energies above 0.5 MeV are. As little as 1 ppm uranium in river waters can be detected, autoradiographs from alpha particles or other radioactivity in body tissues can be made, and personnel radiation exposures as low as 100 kSv (10 Mrem) can be monitored. SSTD badges of DADC polymer for monitoring exposure to high energy radiations are used in sensitive areas. Commercial SSTD films from CR-39 and modifiers of 5 μm and thicker are supplied by Pershore Mouldings Limited, Homalite Company, and Acrylic Company.

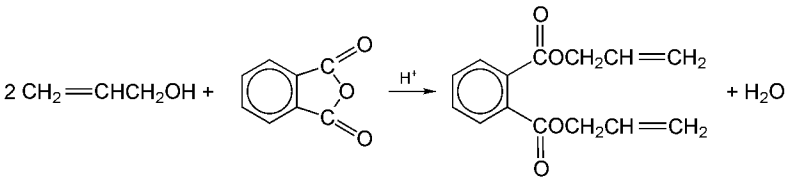
Radiation sensitive cast polymers from DADC are also used in resists for microelectronic circuitry. Relief images result from differential rates of solution in alkali induced by exposure to high energy radiations.

Other Allyl Carbonate Polymers.

In bulk polymerization triallyl carbonates show less than the 13% shrinkage of CR-39 (31). For example, a trimethylolpropane derivative of average molecular weight 300 was treated with phosgene, and the resulting chloroformate, treated with allyl alcohol, gave a polyfunctional allyl carbonate monomer. The purified monomer was heated with a percarbonate initiator to form a polymer lens. Similarly, a propoxylated glycerol derivative of molecular weight ca 700 was treated with phosgene and then with allyl alcohol in the presence of a base (32). A polyfunctional allyl carbonate was prepared from Uvithane 893, an oligomer of molecular weight ca 1300 (33). A copolymer of this monomer with CR-39 had better impact strength than that of the homopolymer. Polymers with 1,4-cyclohexane dimethanol bis(allyl carbonate) have been disclosed (34). A lens prepared from equal parts of this monomer and phenyl methacrylate has a refractive index *n*_D 1.565.

Diallyl Phthalates and Their Polymerization

The three isomeric diallyl phthalates are colorless liquids of mild odor, low volatility, and relatively slow polymerization in the early stages. At ca 25° conversion, the viscous liquid undergoes gelation and polymerization accelerates; however, the last monomer disappears at a slow rate. The monomers are prepared by conventional esterification. Diallyl phthalate (DAP) [131-17-9] is prepared from phthalic anhydride and allyl alcohol:



Properties of two diallyl phthalate monomers, C₁₄H₁₄O₄, are given in Table 5. The liquids are soluble in common organic solvents but insoluble in water.

Table 5. Properties of Commercial Diallyl Esters^a

Property	DAP ^b	DAIP ^c
CAS Registry Number	[131-17-9]	[1087-21-4]
boiling point, °C at 0.53 kPa ^d	161	181
density, g/mL	1.117 ²⁵	1.124 ²⁰
refractive index, n _D ²⁵	1.518	1.5212
surface tension at 20°C, Pa ^e	3.9	3.54
viscosity at 20°C, mPas(cP)	12	17
freezing point, °C	below 70	3
flash point, °C		171
solubility in gasoline at 25°C, %	24	miscible

^a Sources: Osaka Soda Company, Hardwick Chemical Company, and FMC Corporation.
^b Diallyl phthalate.
^c Diallyl isophthalate.
^d To convert kPa to mm Hg, multiply by 7.5.
^e To convert Pa to dyn/cm², multiply by 10.

If DAP is partially polymerized by heating with peroxide initiator to give a viscous solution and the polymerization is terminated with methanol and branched soluble prepolymer precipitated (35), the dried prepolymer melts near 90°C and exhibits about one-third of the unsaturation of the monomer. When bulk polymerization is allowed to continue, gelation occurs at about 25° conversion with very rapid polymerization which, however, stops at 65–93° conversion, depending on the initial benzoyl peroxide concentrations. At higher temperatures cross-linking is less complete. Adding diallyl maleate to DAP delays gelation and gives copolymers.

For all three diallyl phthalate isomers, gelation occurs at nearly the same conversion; DAP prepolymer contains fewer reactive allyl groups than the other isomeric prepolymers (36). More double bonds are lost by cyclization in DAP polymerization, but this does not affect gelation. The heat-distortion temperature of cross-linked DAP polymer is influenced by the initiator chosen and its concentration (37). Heat resistance is increased by electron beam irradiation.

Films from prepolymer solutions can be cured by heating at 150°C. Heating the prepolymer in molds gives clear, insoluble moldings (38). The bulk polymerization of DAP at 80°C has been studied (35). In conversions to ca 25° soluble prepolymer, rates were nearly linear with time and concentrations of benzoyl peroxide. A higher initiator concentration is required than in typical vinyl-type polymerizations.

The bulk polymerization of DAP has been studied at 60°C with azobisisobutyronitrile as initiator (39). Branching of the polymer chains is confirmed by enhanced broadening of the molecular weight distribution until gelation occurred at about 25° conversion. In copolymerizations with styrene at 80°C with benzoyl peroxide as initiator the gel time increases with fraction comonomer in the feed. Both the yield of gel and the styrene units in the gel increase with copolymerization time. Heating DAP prepolymer with styrene in benzene solution at 60–100°C with the initiators gives no gelation, but slow formation of polystyrene and copolymer.

Theoretical calculations to predict the conversions at which gelation of polyfunctional monomers occur are reviewed in reference 40. The gelations of DAP, DAIP, and diallyl terephthalate (DATP) near 25° conversion are little affected by conditions and are much higher than predicted.

DAP Copolymerization. The diallyl phthalates copolymerize readily with monomers bearing strong electron-attracting groups attached to the ethylenic group. These include maleic anhydride, maleate and fumarate esters, and unsaturated polyesters. For example, maleic anhydride copolymerizes with DAP or DAIP in the presence of free-radical initiators at practical rates at ca 50°C; rates are higher than those of the copolymerizations. Additions of styrene, methyl methacrylate, acrylic esters, or acrylonitrile reduce rates of reaction in a linear manner (see Fig. 2). Vinyl chloride, vinyl acetate, or alkenes impede polymerization even more; products are low in comonomer units. Some conjugated comonomers are believed to retard less because they lead to less degradative chain transfer.

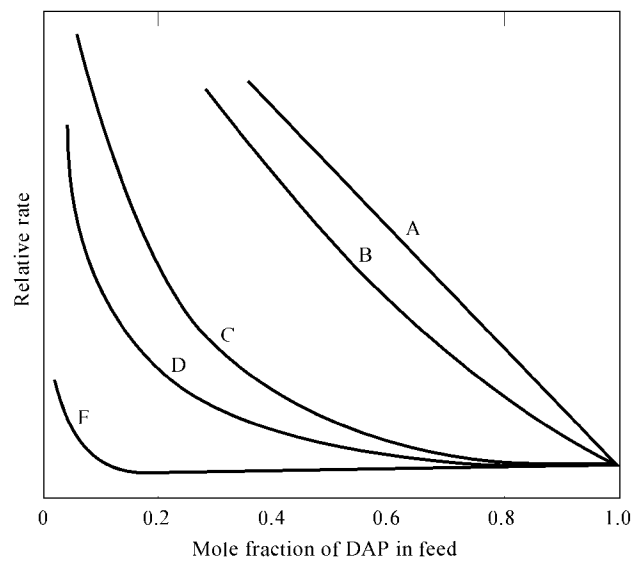


Fig. 2. Relationship between relative rate and monomer composition in the copolymerization of DAP with vinyl monomers: A, styrene or methyl methacrylate; B, methyl acrylate or acrylonitrile; C, vinyl chloride; D, vinyl acetate, and E, ethylene (41).

The Q and e values of the allyl group in DAP have been estimated as 0.029 and 0.04, respectively, suggesting that DAP acts as a fairly typical unconjugated, bifunctional monomer (42). Cyclization affects copolymerization, since cyclized radicals are less reactive in chain propagation. Thus DAP is less reactive in copolymerization than DAIP or DATP where cyclization is sterically hindered. Particular comonomers affect cyclization, chain transfer, and residual unsaturation in the copolymer products. Diallyl tetrachloro- and tetrabromophthalates are low in reactivity.

Diallyl phthalate copolymerizes at 80°C with peroxide catalyst and small amounts of long chain vinyl monomers including vinyl laurate, dioctyl fumarate, lauryl methacrylate, and stearyl methacrylate (43). The products show increased elongations but reduced tensile strengths.

In copolymerization with unsaturated polyesters in fiber-reinforced thermosetting high impact materials, DAP offers advantages over styrene. Glass roving can be immersed in a solution of unsaturated polyester–DAP containing dicumyl peroxide (44). A resin, CaCO_3 , and lubricant are added and the moldings are cured by heating. A solution of DAP prepolymer, benzoyl peroxide, and polyester (from maleic anhydride, phthalic acid, and propylene glycol) in acetone–toluene solution can be impregnated into a nonwoven glass fabric (45), which is cured in decorative panels by heating under pressure. In electronic moldings, polyester, DAP, peroxide, glass fibers, and alumina hydrate are molded by heating at 140°C under pressure (46). In compositions for carbon fiber-reinforced fishing rods DAP is cured with a polyester to give flexural strength as high as 713 MPa (103,000 psi) (47). Prepregs containing DAP, polyester, and mica filler have been applied to electrical coils (48), and other prepregs, containing less DAP, used for decorative panels (49).

Other examples of DAP copolymerizations of industrial interest include copolymerization with MMA in emulsion (50) and for light focusing rods (51); with vinylnaphthalene for lenses (52); with epoxy acrylates and glass fibers (53); epoxy acrylates and coatings (54); with diacetone acrylamide (55); with aliphatic diepoxide compounds (56); triallyl cyanurate in lacquers for printed circuits (57); and DAIP with MMA (58).

Diallyl Isophthalate. DAIP polymerizes faster than DAP, undergoes less cyclization, and yields cured polymers of better heat resistance, eg, up to ca 200°C. Prepolymer molding materials such as Dapon M of FMC, are not sticky. Maleic anhydride accelerates polymerization, whereas vinyl isobutyl ether retards it and delays gelation in castings. Copolymers with maleic anhydride are exceptionally hard and tough and may scratch homopolymer surfaces.

Besides application as heat-resistant molding powders for electronic and other applications, DAIP copolymers have been proposed for optical applications. Lenses of high impact resistance contain 50% DAIP, 20% benzyl methacrylate, and larger amounts of CR-39 (59). A lens of refractive index $n_D = 1.569$ and low dispersion can be cast from phenyl methacrylate, DAIP, and isopropyl peroxide (60). Lenses of better impact properties can be obtained by modifying DAIP with allyl benzoate (61).

Diallyl terephthalate [1026-92-2] is utilized less, but lenses made of copolymers with triallyl cyanurate and methacrylates have been suggested (62). Diallyl tetrabromophthalate and tetrachlorophthalate polymers have been proposed for electronic circuit boards of low flammability (63). They are uv-curable and solder-resistant. Copolymers with unsaturated polyester, vinyl acetate and DAP have been studied (64).

Telomerization. Polymerization of DAP is accelerated by telogens such as CBr_4 , which are more effective chain-transfer agents than the monomer itself (65); gelation is delayed. The telomers are more readily cured in uv than DAP prepolymers. In telomerizations with CCl_4 with peroxide initiator, at a DAP : CCl_4 ratio of 20, the polymer recovered at low conversion has a DP of 12 (66).

Applications. The largest use of diallyl phthalate thermoset polymers is in moldings and coatings for electronic devices requiring high reliability under long-term adverse environmental conditions. These devices include electrical connectors and insulators in communication, computer, and aerospace systems. The flow in molding and curing of these prepolymer formulations must be carefully controlled by selection of initiator, monomer or comonomer content, and heating and radiation. Proprietary compositions may contain about equal weights of prepolymer and filler, eg, fine glass fibers or calcium silicate, 10% antimony oxide, 1–2% DAP or DAIP monomer, silane derivative, peroxide, lubricant, and polymerization-control agents. Formulations are designed for injection, compression, and transfer molding.

For best impact strength, glass fibers should be pretreated with a silane derivative. Fillers may include clays, calcium carbonate, silicates, various silicas, glass, and carbon, preferably as short fibers. Small amounts of metallic stearates or long chain organic acids are added as molding lubricants. In addition to antimony oxide, chlorine- and bromine-containing monomers may be added to reduce flammability. For encapsulation of fragile electronic components, prepolymer of lower molecular weight along with more monomer may be used for flow at low mold pressures. Potting with monomer-polymer syrup is normally too slow. Properties of DAP thermoset moldings are given in Table 6.

Table 6. Properties of DAP Thermoset Moldings^a

Property	ASTM method	Unfilled	Glass-fiber reinforced	Mineral filled
molding temperature, °C		140–190	144–193	133–193
mold shrinkage, cm/cm	D955		0.0005–0.005	0.002–0.007
tensile strength, MPa ^b	D638	27.6	41–76	34–55
flexural strength, MPa ^b	D790	62.0	62–138	55–76
compressive strength, MPa ^b	D695	165	172–241	138–220
elongation, %	D638		3–5	3–5

Izod impact, N per notch ^c	D256A	1.1–1.6	2.1–80	1.6–4.3
hardness, Rockwell	D785	115	E80–87	E61
coefficient of linear expansion, 10 ^{–6} cm/cm per °C	D696		10–36	10–42
deflection temp under 18.2 MPa, °C	D648	155	166–290	162–290
thermal conductivity, W/(m·K)	C177		0.21–0.62	0.29–1.04
refractive index, <i>n</i> _D ²⁶		1.571		
specific gravity	D792		1.70–1.96	1.65–1.85
water absorption ^d , 24 h at 25°C, %	D570	0.20	0.12–0.35	0.2–0.5
dielectric strength ^d , V/mm	D149		16–18	16–18
dielectric constant at 25°C				
10 ³ Hz	3.4	4.4	~4.8	
10 ⁶ Hz	3.4	4.4	~4.4	
arc resistance, s	118	125	140	

^a Ref. 67.
^b To convert MPa to psi, multiply by 145.
^c To convert N per notch to lbf/in. per notch, multiply by 0.187.
^d 3-mm thickness.

Diallyl phthalates are used with glass cloth and roving in tubular ducts, radomes, aircraft, and missile parts of high heat resistance. They offer the advantages of low volatility, little odor, and high heat resistance, replacing styrene with unsaturated polyesters in fiber-reinforced plastic structures. High curing temperatures, however, and high costs limit structures. Glass cloth, textiles, and papers may be impregnated by prepolymer-monomer mixtures in solution along with peroxide initiator and lubricant. Molding and curing gives decorative stain- and heat-resistant overlays for wall panels, tables, and furniture (1).

Favorable rates and yields of DAP prepolymer are obtained by solution polymerization in CCl₄–benzene mixtures (68). Bulk polymerization at 80°C with benzoyl peroxide is advanced to a certain viscosity before addition of ethanol to precipitate the prepolymer that is then dried (69).

Dapon 35 of FMC and a similar Japanese product have been studied by gel permeation chromatography. Hydrogen peroxide acts as a regulator as well as initiator, and gives relatively large fractions of oligomers. In polymerization between 80 and 220°C gelation occurs at 25–45% conversion (70).

Tableware is molded from DAP polymer and prepolymer, cellulose, pigment, dicumyl peroxide, and a silane coupling agent (71). Nontoxic DAP-based polymers have been suggested as being agents of low viscosity and long pot life for glass-reinforced plastics and electroluminescent coatings of high transparency (72). Abrasion-resistant CR-39-DAP copolymer recording disks have low moisture permeability and good heat resistance (73).

Diallyl esters find little application in lenses. However, DAP and DAIP can be polymerized by high energy radiation in lens molds (74). Coatings of silica and alumina by vaporization give antiglare, scratch-resistant lenses.

Other Diallyl Esters

Tables 7 and 8 give properties of some diallyl esters. Dimethallyl phthalate [5085-00-7] has been copolymerized with vinyl acetate and benzoyl peroxide, and reactivity ratios have been reported (75).

Table 7. Properties of Some Diallyl Esters

Diallyl ester	Molecular formula	CAS Registry Number	Bp _{Pa} ^a	<i>n</i> _D ²⁰	<i>d</i> ₄ ²⁰
oxalate	C ₈ H ₁₀ O ₄	[615-99-6]	107 ₁₉	1.4460	1.0081
malonate	C ₉ H ₁₂ O ₄	[1797-75-7]	119 ₁₉	1.4489	1.060
succinate	C ₁₀ H ₁₄ O ₄	[925-16-6]	94 ₀₁₃	1.4507	1.056
adipate	C ₁₂ H ₁₈ O ₄	[2998-04-1]	115 ₀₁₃	1.4542	1.023
sebacate	C ₁₁ H ₂₀ O ₄	[3137-00-6]	164 ₀₂	1.4550	0.978
tartrate	C ₁₀ H ₁₄ O ₆	[57833-54-2]	171 ₁₃	1.187	

^a To convert Pa to mm Hg, multiply by 0.0075.

Table 8. Properties of Allyl–Vinyl Monomers

Property	Allyl methacrylate, AMA	Diallyl maleate, DAM	Diallyl fumarate, DAF
structure	CH₃ CH₂=C—COOA^a	HC—COOA HC—COOA^a	AOOCCH HC—COOA^a
molecular formula	C ₇ H ₁₀ O ₂	C ₁₀ H ₁₂ O ₄	C ₁₀ H ₁₂ O ₄
CAS Registry Number	[96-05-9]	[999-21-3]	[2807-54-7]
boiling point °C _{kPa} ^b	55 ₄	112 ₀₅₃	140 ₀₄₀
density at 25°C, g/cm ³	0.930	1.070	1.0516
refractive index, <i>n</i> _D ²⁶	1.453	1.4664 ^c	1.4669
viscosity mPas (cP)	13	4.3	3.0
flash point, open cup, °C		123	74

^a A allyl CH₂CH=CH₂
^b To convert kPa to mm Hg, multiply by 7.5.
^c At 20°C.

Copolymers of diallyl succinate and unsaturated polyesters cured by x rays provide wear-resistant coatings of MMA dental polymers (76).

Copolymers of diallyl itaconate [2767-99-9] with *N*-vinylpyrrolidinone and styrene have been proposed as oxygen-permeable contact lenses (qv) (77). Reactivity ratios have been studied in the copolymerization of diallyl tartrate (78). A lens of a high refractive index ($n_D = 1.63$) and a heat distortion above 280°C has been reported for diallyl 2,6-naphthalene dicarboxylate [51223-57-5] (79). Diallyl chlorendate [3232-62-0] polymerized in the presence of di-*t*-butyl peroxide gives a lens with a refractive index of $n = 1.57$ (80). Hardness as high as Rockwell 150 is obtained by polymerization of triallyl trimellitate [2694-54-4] initiated by benzoyl peroxide (81).

Among the preformed polymers cured by minor additions of allyl ester monomers and catalysts followed by heat or irradiation are PVC cured by diallyl fumarate (82), PVC cured by diallyl sebacate (83), fluoropolymers cured by triallyl trimellitate (84), and ABS copolymers cured by triallyl trimellitate (85).

In studies of the polymerization kinetics of triallyl citrate [6299-73-6], the cyclization constant was found to be intermediate between that of diallyl succinate and DAP (86). Copolymerization reactivity ratios with vinyl monomers have been reported (87). At 60°C with benzoyl peroxide as initiator, triallyl citrate retards polymerization of styrene, acrylonitrile, vinyl chloride, and vinyl acetate. Properties of polyfunctional allyl esters are given in Table 7; some of these esters have sharp odors and cause skin irritation.

A series of glycol bis(allyl phthalates) and bis(allyl succinates) and their properties are reported in reference 88. In homopolymerizations, cyclization increases in the order: diallyl aliphatic carboxylates < glycol bis(allyl succinates) < glycol bis(allyl phthalates). Copolymerizations with small amounts of DAP can give thermoset moldings of improved impact (89).

Allyl–Vinyl Compounds

Monomers such as allyl methacrylate and diallyl maleate have applications as cross-linking and branching agents selected especially for the different reactivities of their double bonds (90); some physical properties are given in Table 8. These esters are colorless liquids soluble in most organic liquids but little soluble in water; DAM and DAF have pungent odors and are skin irritants.

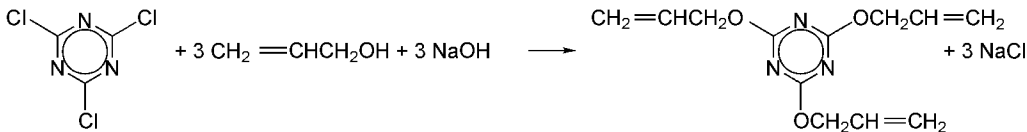
Addition of diallyl fumarates to DAP accelerates polymerization; maximum rates are obtained for 1:1 molar feeds (41). Methyl allyl fumarate [74856-71-6] (MAF), C₈H₁₀O₄, homopolymerizes much faster than methyl allyl maleate [51304-28-0] (MAM) and gelation occurs at low conversion; more cyclization occurs with MAM. The greater reactivity of the fumarate double bond is shown in copolymerization of MAF with styrene in bulk. The maximum rate of copolymerization occurs from monomer ratios, almost 1:1 molar, but no maximum is observed from MAM and styrene. Styrene hinders cyclization of both MAF and MAM.

Diallyl fumarate polymerizes much more rapidly than diallyl maleate. Because of its moderate reactivity, DAM is favored as a cross-linking and branching agent with some vinyl-type monomers (1). Cyclization from homopolymerizations in different concentrations in benzene has been investigated (91). Diallyl itaconate and several other polyfunctional allyl–vinyl monomers are available.

Allyl Methacrylate (AMA). Of the compounds containing both allyl and vinyl-type double bonds, allyl methacrylate is the most important. The lower reactivity of the allyl group permits controlled, second-stage cross-linking when used in low concentrations. A copolymer with MMA in cured moldings has a heat distortion temperature of 96 °C compared to 70°C for MMA homopolymer (92). AMA graft copolymers with acrylate and methacrylate esters blended with PVC and other molding plastics have high impact strength (93). AMA is used as cross-linking agent with methacrylate esters in contact lenses (94). AMA is also used in low concentrations in curable acrylic coatings (95). For cross-linked pressure-sensitive adhesives, a small amount of AMA is used with alkyl acrylates and cured by electron beam irradiation (96). AMA may be added as branching comonomer with acrylic acid for preparing mucilages and thickening agents for aqueous systems (97).

Polyfunctional Allyl Nitrogen Monomers

Triallyl Cyanurate as Cross-linking Agent. Triallyl cyanurate (TAC), 2,4,6-tris(allyloxy)-*s*-triazine [101-37-1], and its isomer triallyl isocyanurate (TAIC) are used as cross-linking agents with comonomers and for aftercuring preformed polymers such as olefin copolymers in electrical insulations. TAC monomer melts at 20–25°C. It is prepared by gradual addition of cyanuric chloride to an excess of allyl alcohol in the presence of aqueous alkali (98).



Properties of TAC and TAIC are given in Table 9.

Table 9. Properties of TAC and TAIC

Property	TAC	TAIC
molecular formula	C ₁₂ H ₁₅ N ₃ O ₃	C ₁₂ H ₁₅ N ₃ O ₃
CAS Registry Number	[101-37-1]	[1025-15-6]
melting point, °C	31	24
boiling point, °C	140 ^a _{7 Pa}	126 ^a _{40 Pa}
density at 30°C, g cm ³	1.1133	1.1720
refractive index n_D^{25}	1.5049	1.5115

^a To convert Pa to mm Hg, multiply by 0.0075.

Crystalline TAC monomer can be stored at room temperature with only slow change, but heating may cause polymerization with violence. In storage, the liquid monomer slowly forms a viscous syrup of prepolymer solution. In homopolymerizations at elevated temperatures with free-radical initiators, two exotherms are observed. An initial release of heat indicates reaction of two allyl groups, a second larger exotherm apparently results from the remaining allyl groups together with rearrangement of the polymer to the more stable isocyanurate structure. Because of brittleness, the homopolymers of TAC and TAIC have had little application.

Triallyl cyanurate is used as a comonomer in small amounts with methacrylate esters and unsaturated polyesters. The addition of 5% or more of TAC to MMA in castings improves heat and solvent resistance as well as thermooxidative stability (99). For optical applications, up to 20% TAC has been suggested. Reactivity ratios for TAC and methacrylate esters have been reported (100).

Small amounts of TAC and TAIC are copolymerized with unsaturated polyesters in glass cloth or fibers in high strength laminates, and electrical sealing and potting applications. In one case, a glass fiber mat impregnated with a mixture of a maleate polyester, DAP, and TAC was cured with *t*-butyl peroxide at 150°C (101). Solid unsaturated polyesters with 4% TAC have been used in powder coating formulations cured by heating with *t*-butyl perbenzoate and cobalt octanoate (102). Allyl cyanoacrylate modified by TAC has been used in dental adhesives (103).

Triallyl Cyanurate Cure of Preformed Polymers. TAC and TAIC are often used in small amounts with vinyl-type and condensation polymers for cured plastics, rubber and adhesive products of high strength, and heat and solvent resistance. In some cases, chemical stability is also

improved. These effects are the result of grafting at active H atoms as well as penetrating the polymer network. Improvement in strength of PVC by addition of TAC is discussed in reference 104. The modification of PVC by increasing proportions of TAC and diallyl sebacate (DAS) has been studied (105). Up to about 15% TAC, graft polymerization predominates, whereas with higher concentrations polymer networks are observed. DAS is less effective in forming such networks. Both comonomers have a stabilizing effect against loss of HCl under exposure to gamma radiation (106); decomposition products have been studied (107). TAC may act also as sensitizer and stabilizer in electron radiation curing (qv) of PE, PP, and PVC. TAC has been applied to curing PVC elastomers (108).

The use of TAC as a curing agent continues to grow for polyolefins and olefin copolymer plastics and rubbers. Examples include polyethylene (109), chlorosulfonated polyethylene (110), polypropylene (111), ethylene–vinyl acetate (112), ethylene–propylene copolymer (113), acrylonitrile copolymers (114), and methylstyrene polymers (115). In ethylene–propylene copolymer rubber compositions. TAC has been used for injection molding of fenders (116). Unsaturated elastomers, such as EPDM, cross link with TAC by hydrogen abstraction and addition to double bonds in the presence of peroxyketal catalysts (117) (see ELASTOMERS, SYNTHETIC).

For curing copolymers of tetrafluoroethylene and perfluorovinyl ether, addition of ca 4% TAC has been proposed (118). TFE–propylene copolymers have been cured by TAC and organic peroxide (119). Copolymers of TFE-propylene-vinylidene fluoride are cured with TAC by heating at 200°C.

Nonvinyl polymers cured by TAC include polyamides (120), polyamide–polyurethane blends (121), caprolactone polymers (122), terephthalate polymers (123), epoxy resins (124), and acrylic epoxies (125).

TAIC as Curing Agent. Triallyl isocyanurate is prepared from an alkali cyanate with allyl chloride. Homopolymers are brittle, intractable, and of little use. A viscous solution of prepolymer first forms under mild polymerization conditions. Addition of alcohol to benzoyl peroxide-catalyzed syrup gives a solid prepolymer of molecular weight 5800 (126). TAIC prepolymer of molecular weight 6000 cures faster than DAP prepolymer (127). TAIC with methacrylic acid in aqueous solution along with azobisisobutyronitrile gives, at first, soluble polymers which cross link on further conversion (128). Zinc chloride accelerates polymerization rates of TAIC (129). Copolymers have been prepared with diallylamine and chloroprene (130).

Small amounts of TAIC together with DAP have been used to cure unsaturated polyesters in glass-reinforced thermosets (131). It has been used with polyfunctional methacrylate esters in anaerobic adhesives (132). TAIC and vinyl acetate are copolymerized in aqueous suspension, and vinyl alcohol copolymer gels are made from the products (133). Electron cure of poly(ethylene terephthalate) moldings containing TAIC improves heat resistance and transparency (134).

Publications on curing polymers with TAIC include TFE–propylene copolymer (135), TFE–propylene–perfluoroallyl ether (136), ethylene–chlorotrifluoroethylene copolymers (137), polyethylene (138), ethylene–vinyl acetate copolymers (139), polybutadienes (140), PVC (141), polyamide (142), polyester (143), poly(ethylene terephthalate) (144), siloxane elastomers (145), maleimide polymers (146), and polyimide esters (147).

Diallyl Ammonium Polymers. *N,N*-Diallyldimethyl(DADM)ammonium salts are used for the preparation of polyelectrolytes. Polymerization from concentrated water solution can be initiated by *t*-butyl hydroperoxide (148). The polymers are used as flocculating agents, and in water purification (1). The polyelectrolytes are used for aqueous coal flotation (149). Copolymers of DADM ammonium chloride with acrylamide have also been proposed for water purification (150). DADM ammonium polyelectrolyte is used in coatings for copy paper (151). Electrical conductivity of the polyelectrolytes plasticized with poly(ethylene glycol) has been studied (152), and microencapsulation of polyelectrolytes such as DADM ammonium chloride has been reported (153). DADM ammonium compounds can be used as cross-linking agents for temporary gel-blocking in petroleum and natural gas wells (154).

Copolymers of diallyldimethylammonium chloride [7398-69-8] with acrylamide have been used in electroconductive coatings (155). Copolymers with acrylamide made in activated aqueous persulfate solution have flocculating activity increasing with molecular weight (156). DADM ammonium chloride can be grafted with cellulose from concentrated aqueous solution; catalysis is by ammonium persulfate (157). Diallyl didodecylammonium bromide [96499-24-0] has been used for preparation of polymerized vesicles (158).

Molded polyamide surfaces can be hardened by grafting with *N,N*-diallylacrylamide [3085-68-5] monomer under exposure to electron beam (159). *N,N*-Diallyltartardiamide [58477-85-3] is a cross-linking agent for acrylamide reversible gels in electrophoresis. Such gels can be dissolved by a dilute periodic acid solution in order to recover protein fractions.

Other Allyl Compounds

Although much research has been carried out with allyl ethers there has been only limited commercial use (1). Multifunctional allyl glycidyl ether [106-92-3], CH2=CHCH2OCH2CH(O)CH2, a toxic liquid, has been used as an additive to epoxy resins, in copolymers with ethylene oxide and derivatives, and in copolymers with vinyl comonomers. The second reactive group permits final cross-linking with radiation or heating with peroxides.

A great number of other allyl compounds have been prepared, especially allyl ethers and allyl ether derivatives of carbohydrates and other polymers. They are made by the reaction of hydroxyl groups with allyl chloride in the presence of alkali (1). Polymerizations and copolymerizations are generally slow and incomplete. Products have only limited use in coatings, inks, and specialties. Properties of a few allyl ethers are given in Table 10.

Table 10. Physical Properties of Some Diallyl Ethers

Ether	Molecular formula	CAS Registry Number	Bp, °C ^a	Sp gr ²⁰ ₂₀	<i>n</i> ²⁰ _D
diallyl ether	C ₆ H ₁₀ O	[557-40-4]	96	0.805	1.4165
allyl methallyl ether	C ₇ H ₁₂ O	[14289-96-4]	115		1.4236
1,2-diallyloxyethane	C ₈ H ₁₄ O ₂	[7529-27-3]	37 ₁₃₃ Pa	0.894	1.4340
1,2-dimethallyloxyethane	C ₁₀ H ₁₈ O ₂	[79719-27-0]	50 ₃₃₂ Pa	0.8779	1.4383
trimethylolpropane diallyl ether	C ₁₂ H ₂₂ O ₃	[682-09-7]	258	0.957	1.4560
pentaerythritol diallyl ether	C ₁₁ H ₂₀ O ₄	[2590-16-1]	174 _{13k} Pa	1.037	1.4695

^a To convert Pa to mm Hg, multiply by 0.0075.

These compounds are miscible with most organic solvents. Much research has been directed toward the preparation of air-drying prepolymers or oligomers. Thus allyl groups have been introduced into low molecular weight polyesters, polyurethanes, and formaldehyde condensates (1), but curing rates have been low. Some examples include copolymers of trimethylolpropane diallyl ether with unsaturated polyesters in uv-curable coatings (160). A bis(allyloxy)sulfolane can be used to cross-link unsaturated polyesters in coatings (161). Pentaerythritol triallyl ether [1471-17-6] serves as a curing agent in acrylic photolacquers (162). Diallyl ether reacts with SO₂ to give soluble copolymers containing cyclic structures (163).

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ALUMINUM AND ALUMINUM ALLOYS

Aluminum [7429-90-5], Al, is a silver-white metallic element in group III of the periodic table having an electronic configuration of $1s^22s^22p\ 3s^23p^1$. Aluminum exhibits a valence of +3 in all compounds except for a few high temperature gaseous species in which the aluminum may be monovalent or divalent. Aluminum is the most abundant metallic element on the surfaces of the earth and moon, comprising 8.8% by weight (6.6 atomic %) of the earth's crust. However, it is rarely found free in nature. Nearly all rocks, particularly igneous rocks, contain aluminum as aluminosilicate minerals.

Although impure metallic aluminum was isolated in 1824 by reducing aluminum chloride [7446-70-0], $AlCl_3$, using potassium amalgam, Wöhler, who produced higher purity aluminum by a similar method in 1827 and determined its properties, is often given the credit for the discovery. The metal remained a laboratory curiosity until 1854 when the method of preparation was improved, using sodium as a reductant, and commercial quantities of relatively pure aluminum were produced. The present industrial production method was developed independently in 1886 by both Paul-Louis Héroult in France and Charles Martin Hall in Oberlin, Ohio.

Aluminum reflects radiant energy throughout the spectrum. It is odorless, tasteless, nontoxic, and nonmagnetic. Because of its many desirable physical, chemical, and metallurgical properties, aluminum is the most widely used nonferrous metal. The utility of the metal is enhanced by the formation of a stable adherent oxide surface that resists corrosion. Because of high electrical conductivity and lightness, aluminum is used extensively in electrical transmission lines. High purity aluminum is soft and lacks strength but its alloys, containing small amounts of other elements, have high strength-to-weight ratios. Alloys of aluminum are readily formable by many metalworking processes; they can be joined, cast, or machined and accept a wide variety of finishes. Aluminum, having a density about one-third that of ferrous alloys, is used in transportation and structural applications where weight saving is important.

Physical Properties

The properties of aluminum vary significantly according to purity and alloying (1). Physical properties for aluminum of a minimum of 99.99% purity are summarized in Table 1. Although a number of radioactive isotopes have been artificially produced (see RADIOISOTOPES), naturally occurring aluminum consists of a single stable isotope, ^{27}Al having a cross section for thermal neutrons of $0.215 \times 10^{-28}\ m^2$. This low cross section and the short half-life of the radioactive product from neutron irradiation make aluminum an attractive material for use within nuclear reactors. Aluminum crystallizes in the face-centered cubic system having a unit cell of 0.40496 nm at 20°C. The unit cell contains four atoms and has a coordination number of 12. The distance of closest approach of atoms is 0.2863 nm. The effects of temperature on the density of aluminum are shown in Table 2. The change in density at the solid–liquid transformation corresponds to a volume increase of ca 6.5%. The heat capacities of solid and liquid aluminum are shown in Table 3. Other thermodynamic data are available in reference 3.

Table 1. Physical Properties of Aluminum

Property	Value
atomic number	13
atomic weight	26.9815
density at 25°C, kg m ³	2698
melting point, °C	660.2
boiling point, °C	2494
thermal conductivity at 25°C, W (m·K)	234.3
latent heat of fusion, J g ^a	395
latent heat of vaporization at bp ΔH_v , kJ g ^a	10,777
electrical conductivity	65% IACS ^b
electrical resistivity at 20°C $\Omega\cdot m$	2.6548×10^{-8}
temperature coefficient of electrical resistivity, $\Omega\cdot m\ ^\circ C$	0.0043
electrochemical equivalent, mg $^\circ C$	0.0932
electrode potential, V	1.66
magnetic susceptibility, g ⁻¹	0.6276×10^{-6}
Young's modulus, MPa ^c	65,000
tensile strength, MPa ^c	50

^a To convert J to cal, divide by 4.184.
^b International Annealed Copper Standard.
^c To convert MPa to psi, multiply by 145.

Table 2. Density of 99.996% Aluminum

Temperature, °C	Density, kg m ³
<i>Solid</i>	
25°C	2698
100°C	2680 ^a
300°C	2660 ^a
500°C	2620 ^a
660°C	2550 ^a
<i>Liquid</i> ^b	
660°C	2368

700°C	2357
750°C	2345
800°C	2332
850°C	2319
900°C	2304

^a Calculated from density at 25 °C and volume expansion at elevated temperatures.

^b Ref. 2.

Table 3. Heat Capacity of Aluminum ^a

Temperature, K	Heat capacity, J (kg·K) ^b
<i>Crystalline solid</i>	
0 K	0.00
100 K	481.7
200 K	790.8
298 K	897.2
300 K	898.7
400 K	955.6
500 K	994.8
600 K	1033.5
700 K	1078.5
800 K	1132.7
900 K	1197.4
<i>Liquid</i>	
1000 and higher K	1273.5

^a Ref. 3.

^b To convert J to cal, divide by 4.184.

The linear expansion of aluminum over several temperature ranges can be calculated from equations 1–3

$$L_t(\text{ }-200\text{ to }0^{\circ}\text{C}) = L_0\big[1 + C\big(21.57t + 0.00443t^2 - 0.000124t^3\big) \cdot 10^{-6}\big]$$

(1)

$$L_t(\text{ }-60\text{ to }100^{\circ}\text{C}) = L_0\big[1 + C\big(22.17t + 0.012t^2\big) \cdot 10^{-6}\big]$$

(2)

$$L_t(0\text{ to }500^{\circ}\text{C}) = L_0\big[1 + C\big(22.34t + 0.00997t^2\big) \cdot 10^{-6}\big]$$

(3)

where L_0 = length at 0°C, L_t = length at temperature t , and C = alloy constant, which is unity for pure aluminum. The thermal conductivity of aluminum at various temperatures is shown in Table 4. The thermal and electrical conductivities are related by

$$K = 2.1\lambda T \cdot 10^{-6} + 12.55$$

(4)

where K = thermal conductivity in W/(m·K), λ = electrical conductivity in S/m (or reciprocal Ω·m), and T = temperature K. The electrical resistivity of aluminum of 99.996% purity is 2.6548×10^{-8} Ω·m at 20°C and the temperature coefficient of electrical resistivity is 0.0043 Ω·m/°C. The effects of temperature on electrical resistivity for solid and liquid aluminum are shown in Table 5. Aluminum becomes superconductive at temperatures near absolute zero and has a transition temperature of 1.187 K. Resistivity at very low temperatures is strongly increased by impurities.

Table 4. Thermal Conductivity of Aluminum

Temperature, K	Thermal conductivity, W/(m·K)	
	99.996% Al ^a	99.95% Al ^b
4 K	3150.6	
6 K	4196.6	
8 K	5196.5	
10 K	5995.7	
15 K	6794.8	
20 K	5497.8	
50 K	949.8	
100 K	301.2	
150 K	244.7	
200 K	234.3	
300 K	234.3	
298 K		225.1
523 K		203.3
723 K		189.9
923 K		186.2
1013 K		59.8 ^c
1173 K		75.3 ^c

^a Ref. 4.

^b Ref. 5.

^c Liquid aluminum.

Table 5. Electrical Resistivity of Aluminum

Temperature, °C	Resistivity, Ωm × 10 ⁻⁸
<i>Solid</i> ^a	
0°C	2.42
100°C	3.50
200°C	4.63
300°C	5.81
400°C	7.05
500°C	8.36
600°C	9.77
650°C	10.56
<i>Liquid</i> ^b	
660°C	24.20
700°C	24.75
800°C	26.25
1000°C	29.20
1200°C	32.15

^a Ref. 6.

^b Ref. 7.

Optical Properties. The index of refraction and extinction coefficient of vacuum-deposited aluminum films have been reported (8,9) as have the total reflectance at various wavelengths and emissivity at various temperatures (10). Emissivity increases significantly as the thickness of the oxide film on aluminum increases and can be 70–80% for oxide films of 100 nm.

Solution Potential. The standard electrode potential of aluminum ($\text{Al} \rightarrow \text{Al}^{3+} + 3\text{e}^-$) is −1.66 V on the standard hydrogen scale and −1.99 V on the 0.1 N calomel scale at 25°C. In the electromotive force series this places aluminum cathodic to magnesium and anodic to zinc, cadmium, iron, nickel, and copper. Aluminum electrode potentials are irreversible in aqueous solutions and vary significantly with pH. Potentials measured in highly basic solutions are anodic to those measured in acid solutions.

Surface Tension and Viscosity. The surface tension of molten aluminum, determined by the method of maximum bubble pressure, is $0.86 \pm 0.2 \text{ N/m}$ (860 dyn/cm) in the range of 700–750°C. The viscosity of 99.996% aluminum at these same temperatures is 1–1.2 mPa·s (1–1.2 cP).

Aluminum and Hydrogen. Hydrogen [1333-74-0], H₂, is the only gas known to be appreciably soluble in solid or molten aluminum. Hydrogen can be introduced into liquid aluminum from reaction with moisture present in the furnace atmosphere or the refractories, or with moisture entrapped in the oxide film of the solid aluminum before melting. The solubility of hydrogen in molten and solid aluminum is shown in Table 6.

Table 6. Solubility of Hydrogen in Aluminum

Temperature, °C	Solubility ^a , mL H ₂ /100 g Al	
	Reference 11	Reference 12
<i>Solid</i>		
400°C	0.004	0.003
500°C	0.01	0.01
600°C	0.025	0.03
660°C	0.04	0.05
<i>Liquid</i>		
660°C	0.69	0.46
700°C	0.91	0.63
800°C	1.68	1.23
850°C	2.18	1.66

^a Values at 20°C and 202.3 kPa (14.7 psi); pressure of hydrogen over sample is 101.3 kPa (1 atm).

Chemical Properties

Reactions with Elements and Inorganic Compounds. Aluminum reacts with oxygen [7782-44-7], O₂, having a heat of reaction of 1675.7 kJ/mol (400.5 kcal/mol) Al₂O₃ produced.



In dry air at room temperature this reaction is self-limiting, producing a highly impervious film of oxide ca 5 nm in thickness. The film provides both stability at ambient temperature and resistance to corrosion by seawater and other aqueous and chemical solutions. Thicker oxide films are formed at elevated temperatures and other conditions of exposure. Molten aluminum is also protected by an oxide film and oxidation of the liquid proceeds very slowly in the absence of agitation.

At high temperatures, aluminum reduces many oxygen-containing compounds, particularly metal oxides. These reactions, of the type shown in equation 6, are used in the manufacture of certain metals and alloys, as well as in the thermite welding process.



Molten aluminum reacts violently with water [7732-18-5] and the molten metal should not be allowed to touch damp tools or containers. In finely divided powder form, aluminum also reacts with boiling water to form hydrogen and aluminum hydroxide [21645-51-2]; this reaction proceeds slowly in cold water.

Aluminum does not combine directly with hydrogen, but it does react with nitrogen [7727-37-9], N₂, sulfur [7704-34-9], and carbon [7440-44-0] in

oxygen-free atmospheres at high temperatures. To form aluminum carbide [1299-86-1], Al₄C₃, temperatures above 1000°C are required. Aluminum nitride [24304-00-5], AlN, is produced by arcing high purity aluminum electrodes in a nitrogen atmosphere. Aluminum sulfide [1302-81-4], Al₂S₃, and aluminum phosphide [20859-73-8], AlP, result from reaction at high temperatures with sulfur and phosphorus [7723-14-0], respectively.

Very high purity aluminum, resistant to attack by most acids, is used in the storage of nitric acid, concentrated sulfuric acid, organic acids, and other chemical reagents. Aluminum is, however, dissolved by aqua regia. Because of its amphoteric nature, aluminum is attacked rapidly by solutions of alkali hydroxides evolving hydrogen and forming soluble aluminates. Aluminum reacts vigorously with fluorine [7782-41-4], chlorine [7782-50-5], bromine [7726-95-6], and iodine [7553-56-2] to form trihalides, and with chlorinated hydrocarbons in the presence of water. It also reacts to form a volatile aluminum chloride when heated in a current of dry oxygen-free chlorine or hydrogen chloride. Gaseous monohalides can be formed by passing the trihalides over aluminum at temperatures above 800°C



Aluminum hydroxide and aluminum chloride do not ionize appreciably in solution but behave in some respects as covalent compounds. The aluminum ion has a coordination number of six and in solution binds six molecules of water existing as [Al(H₂O)]³⁺. On addition of a base, substitution of the hydroxyl ion for the water molecule proceeds until the normal hydroxide results and precipitation is observed. Dehydration is essentially complete at pH 7.

Aluminum is attacked by salts of more noble metals. In particular, aluminum and its alloys should not be used in contact with mercury [7439-97-6] or mercury compounds.

Reaction with Organic Compounds. Aluminum is not attacked by saturated or unsaturated, aliphatic or aromatic hydrocarbons. Halogenated derivatives of hydrocarbons do not generally react with aluminum except in the presence of water, which leads to the formation of halogen acids. The chemical stability of aluminum in the presence of alcohols is very good and stability is excellent in the presence of aldehydes, ketones, and quinones.

Organic compounds that form with aluminum other than through a direct metal-to-carbon bond include the metallo-organics, represented as Al-X-R where X may be oxygen, nitrogen, or sulfur, and R is a suitable organic radical. The alcoholates or alkoxides are compounds of this type where R is an alcohol (see ALKOXIDES, METAL). Compounds having an aluminum-to-carbon bond include polymers that may be linear or cross-linked. They are best described as vinyl, divinyl, and trivinyl aluminum halides that polymerize rapidly to compounds the structures of which are not completely understood. Aluminum alkyls are also aluminum-carbon bond compounds. These are not polymeric but are viewed as being bridge compounds of varying complexity. Alkylaluminum compounds are used as catalysts in the preparation of oriented crystalline polyolefins leading to the production of elastomers that are essentially identical in structure to natural rubber (see ELASTOMERS, SYNTHETIC).

Manufacture and Processing

Raw Materials. Aluminum, the third most abundant element in the earth's crust, is usually combined with silicon and oxygen in rock. When aluminum silicate minerals are subjected to tropical weathering, aluminum hydroxide may be formed. Rock that contains high concentrations of aluminum hydroxide minerals is called bauxite [1318-16-7]. Although bauxite is, with rare exception, the starting material for the production of aluminum, the industry generally refers to metallurgical grade alumina [1344-28-1], Al₂O₃, extracted from bauxite by the Bayer Process (see ALUMINUM COMPOUNDS), as the ore. Aluminum is obtained by electrolysis of this purified ore. The specification of metallurgical alumina is given in Table 7.

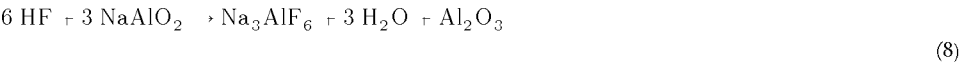
Table 7. Properties of Metallurgical Grade Alumina

Item	Influencing operations ^a		Normal range	Specifications	
	Major	Minor		Typical	Desirable
particle size, μm	P	Ca	10–200	<10% > 150 <10% < 44	<2% > 150 <2% < 20
chemical composition					
Na ₂ O	P	Ca	0.3–0.7 ^o o	<0.5%	0.35 ^o o
Fe ₂ O ₃	D	Cl	0.01–0.04 ^o o	<0.03%	<0.015%
SiO ₂	D		0.01–0.03 ^o o	<0.025%	<0.020
CaO	D,Cl		0.02–0.08 ^o o	<0.06%	<0.030
TiO ₂			0.002–0.005 ^o o	<0.005%	0.002
CuO			0.001–0.01 ^o o	<0.01%	
K ₂ O			0.000–0.05 ^o o	<0.005%	
MgO				<0.002%	
P ₂ O ₅				<0.001%	
NiO				<0.005%	
Cr ₂ O ₃				<0.002%	
LOI ^b			0.3–1.5 ^o o		
total water			1.5–4.0 ^o o	3.5 ^o o	
surface area, m ² g			20–100	60	80
α-Al ₂ O ₃	Ca		5–90 ^o o	40 ^o o	10 ^o o
attrition index	P,Ca		4–15		8
crystallite size, μm	P		10–200		20
angle of repose, deg	Ca		30–45		35
bulk density, kg m ⁻³					
loose			800–1100		
packed			950–1300		

^a Designations are as follows: Ca calcination, Cl clarification, D digestion, and P precipitation.

^b LOI loss on ignition.

Cryolite. Cryolite [15096-52-3], Na₃AlF₆, is the primary constituent of the Hall-H roult cell electrolyte. High purity, natural cryolite is found in Greenland, but its rarity and cost have caused the aluminum industry to substitute synthetic cryolite. The latter is produced by the reaction of hydrofluoric acid [7664-39-3], HF, with sodium aluminate [1302-42-7], NaAlO₂, from the Bayer process



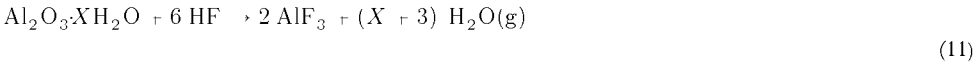
Gaseous hydrofluoric acid is generally made by the reaction of acid-grade fluorspar [14542-23-5], CaF_2 , with sulfuric acid (see FLUORINE COMPOUNDS, INORGANIC)



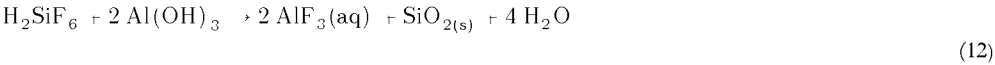
No cryolite is actually needed once the smelting process is in operation because cryolite is produced in the reduction cells by neutralizing the Na_2O brought into the cell as an impurity in the alumina using aluminum fluoride.



Thus operating cells need aluminum fluoride [7784-18-1], AlF_3 , rather than cryolite. Much aluminum fluoride is produced in a fluidized bed by the reaction of hydrofluoric acid gas and activated alumina made by partially calcining the alumina hydrate from the Bayer process



Aluminum fluoride is also made by the reaction of fluosilicic acid [16961-83-4], H_2SiF_6 , a by-product from phosphoric acid production (see PHOSPHORIC ACID AND THE PHOSPHATES), and aluminum hydroxide from the Bayer process.



The AlF_3 solution is filtered, AlF_3 precipitated by heating, flash dried, and calcined.

The equivalent of 3–4 kg of F per metric ton of aluminum produced is adsorbed from the bath into the cell lining over the lining's life (3–10 yr). The recoverable fluoride, 70–75%, requires an expensive recovery plant justified largely on an ecological basis. The most common method of recovery treats the crushed lining using dilute NaOH to dissolve the cryolite and other fluorides. The solution is filtered and the $\text{NaF}:\text{AlF}_3$ mol ratio adjusted to 3:1 whereupon Na_3AlF_6 is precipitated by neutralizing the NaOH using CO_2 .

Fluoride Availability. The aluminum industry in the United States uses about 15 kg of fluoride ion per metric ton aluminum, 10–25% of which is lost. The remainder, consisting of cryolite generated in reduction cells and of bath in scrap cell linings, is stored for future use. New fluoride for the aluminum industry comes largely from fluorspar, the world reserves of which are widespread and abundant (see FLUORINE COMPOUNDS, INORGANIC). Fluoride is also recovered from phosphate rock, generally as fluosilicic acid, in producing phosphoric acid. Mexico, the world's largest producer of fluorspar, supplies over 20% of the world's demand and 75% of U.S. usage. The aluminum industry uses about 21% of the fluoride consumed in the United States. Improved emission control (see EXHAUST CONTROL, INDUSTRIAL) and recycling of fluorides continue to reduce the fluoride requirements of the aluminum industry.

Electrolysis of Alumina. Since the discovery of the process by Hall and H roult, nearly all aluminum has been produced by electrolysis of alumina dissolved in a molten cryolite based bath. The aluminum is deposited molten on a carbon cathode, which serves also as the melt container. Simultaneously, oxygen is deposited on and consumes the cell's carbon carbon anode(s) (13). Pure cryolite melts at 1012 C, but alumina and additives, namely 4–8% calcium fluoride [7789-75-5], CaF_2 , 5–13% aluminum fluoride, 0–7% lithium fluoride [7789-24-4], LiF and 0–5% magnesium fluoride [7783-40-6], MgF_2 , lower the melting point, allowing operation at 920–980 C. The system $\text{Na}_3\text{AlF}_6\text{--Al}_2\text{O}_3$ (Fig. 1) has a eutectic at 10.5 wt % Al_2O_3 at 960 C (14). Figure 2 gives liquidus temperatures in the system $\text{Na}_3\text{AlF}_6\text{--AlF}_3\text{--Al}_2\text{O}_3$ (15). Equations for the liquidus temperature and alumina solubility have also been worked out for the $\text{Na}_3\text{AlF}_6\text{--LiF--CaF}_2\text{--AlF}_3\text{--Al}_2\text{O}_3$ system (16). Joule heat from the flow of electric current is more than adequate to maintain the melt temperature.

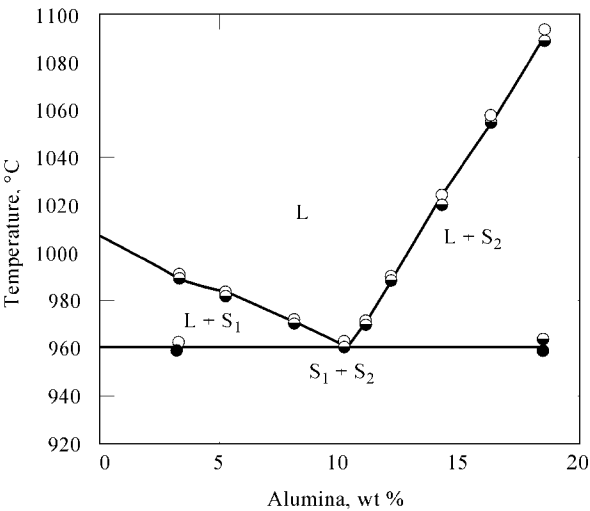


Fig. 1. Cryolite–alumina phase diagram from 0 to 18.5% alumina. L, liquid; S₁, cryolite; S₂, corundum;  , liquid;  , liquid and solid;  , solid (14).

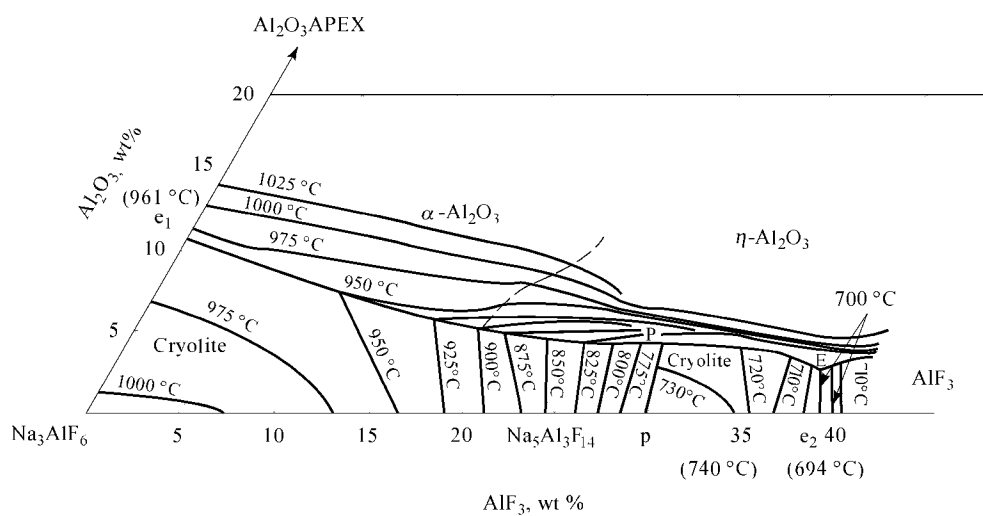


Fig. 2. The system $\text{Na}_3\text{AlF}_6 - \text{AlF}_3 - \text{Al}_2\text{O}_3$; P, ternary peritectic point ($28.3^\circ \text{ AlF}_3 - 4.4^\circ \text{ Al}_2\text{O}_3 - 67.3^\circ \text{ Na}_3\text{AlF}_6$, 723°C); E, ternary eutectic point ($37.3^\circ \text{ AlF}_3 - 3.2^\circ \text{ Al}_2\text{O}_3 - 59.5^\circ \text{ Na}_3\text{AlF}_6$, 684°C); p, binary peritectic point; e, e₁, binary points (15).

Although the mechanism of electrolysis is still imperfectly understood, most investigators (17) agree that cryolite ionizes as



Alumina dissolves at low concentrations by forming oxyfluoride ions having a 2:1 ratio of aluminum to oxygen ($\text{Al}_2\text{OF}_4^{2-}$),

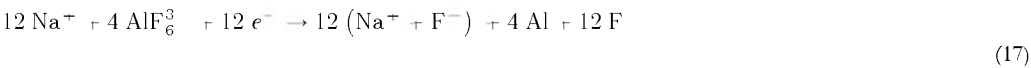


for example, at higher alumina concentrations, oxyfluoride ions with a 1:1 ratio of aluminum to oxygen ($\text{Al}_2\text{O}_2\text{F}_4^{2-}$) are formed (18)

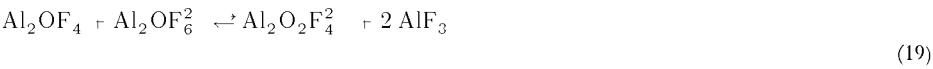
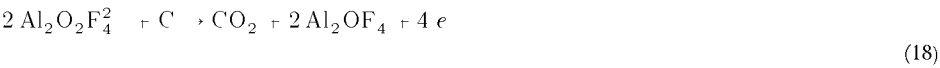


Cells are generally operated using 1.5–6 wt % Al_2O_3 in the electrolyte. Saturation ranges between 6–12% Al_2O_3 depending upon composition and temperature.

Ion transport measurements indicate that Na^+ ions carry most of the current, yet aluminum is deposited. A charge transfer probably occurs at the cathode interface and hexafluoroaluminate ions are discharged, forming aluminum and F^- ions to neutralize the charge of the current carrying Na^+



Oxyfluoride ions are discharged at the anode, forming carbon dioxide [124-38-9] and aluminum fluoride. The first oxygen can be removed more readily from $\text{Al}_2\text{O}_2\text{F}_4^{2-}$ than either the second or the oxygen from $\text{Al}_2\text{OF}_4^{2-}$



Combining alumina dissolution, equation 16, and the anode and cathode reactions, equations 17–19, gives the overall reaction



According to Faraday's law, one Faraday (26.80 Ah) should deposit one gram equivalent (8.994 g) of aluminum. In practice only 85–95% of this amount is obtained. Loss of Faraday efficiency is caused mainly by reduced species (Al , Na , or AlF) dissolving or dispersing in the electrolyte (bath) at the cathode and being transported toward the anode where these species are reoxidized by carbon dioxide forming carbon monoxide and metal oxide, which then dissolves in the electrolyte. Certain bath additives, particularly aluminum fluoride, lower the content of reduced species in the electrolyte and thereby improve current efficiency.

Equipment. A modern alumina smelting cell consists of a rectangular steel shell typically 9–16 m × 3–4 m × 1–1.3 m. It is lined with refractory insulation that surrounds an inner lining of baked carbon (see CARBON ARTIFICIAL GRAPHITE). Few materials other than carbon are able to withstand the combined corrosive action of molten fluorides and molten aluminum. Thermal insulation is adjusted to provide sufficient heat loss to freeze a protective coating of electrolyte on the inner walls but not on the bottom, which must remain substantially bare for electrical contact to the molten aluminum cathode. Steel (collector) bars are joined to the carbon cathode at the bottom to conduct electric current from the cell. Current enters the cell either through prebaked carbon anodes (Fig. 3) or through a continuous self-baking Soderberg anode (Fig. 4).

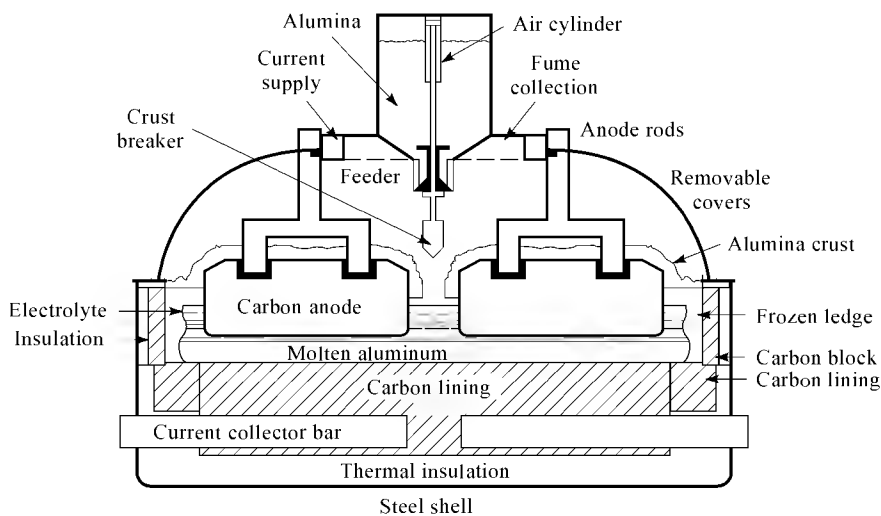


Fig. 3. Aluminum electrolyzing cell with prebaked anode.

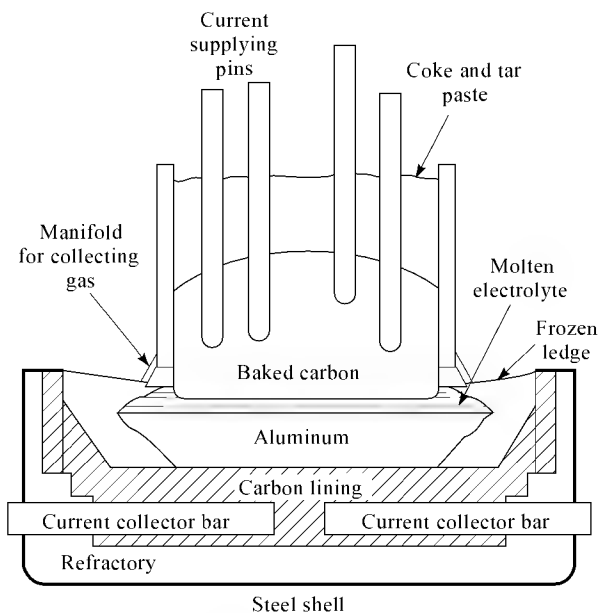


Fig. 4. Aluminum electrolyzing cell with Soderberg anode.

Prebaked anodes are produced by molding petroleum coke and coal tar pitch binder into blocks typically 70 cm × 125 cm × 50 cm, and baking to 1000–1200°C. Petroleum coke is used because of its low impurity (ash) content. The more noble impurities, such as iron and silicon, deposit in the aluminum whereas less noble ones such as calcium and magnesium, accumulate as fluorides in the bath. Coal-based coke could be used, but extensive and expensive prepurification would be required. Steel stubs seated in the anode using cast iron support the anodes (via anode rods) in the electrolyte and conduct electric current into the anodes (Fig. 3). Electrical resistivity of prebaked anodes ranges from 5–6 Ωm; anode current density ranges from 0.65 to 1.3 A cm².

A Soderberg anode is formed continuously from a paste of petroleum coke and coal tar pitch added to the top of a rectangular steel casing typically 6–8 m × 2 m × 1 m (Fig. 4). While passing through the casing, the paste bakes forming carbon to replace the anode being consumed. The baked portion extends past the casing and into the molten electrolyte. Electric current enters the anode through vertical or sloping steel spikes (also called pins). Periodically, the lowest spikes are reset to a higher level. Resistivity of Soderberg anodes is about 30% higher than prebaked anodes. Current density is lower, ranging from 0.65 to 0.9 A cm².

Molten aluminum is removed from the cells by siphoning, generally daily, into a crucible. Normally the metal is 99.6–99.9% pure. The principal impurities are Fe, Si, Ti, V, and Mn, and come largely from the anode, but also from the alumina.

Energy Considerations. Table 8 gives a breakdown of the energy required to produce aluminum. Note that smelting consumes about 65% of the required energy. In the United States most of this energy comes from fossil fuels. Hydropower which supplies 33% for smelting and 17% for fabricating, is not used for mining and refining; little nuclear power is used.

Table 8. Energy Consumption Per Metric Ton of Aluminum Produced^a

Operation	Thermal, MJ ^b	Electric, kWh	Total energy	
			Fossil and hydro, MJ ^b	If all fossil, MJ ^b
mining and refining	30,000	480	35,200	35,200
smelting	19,000 ^c	15,000	146,400	182,500
mill processing	19,000	1,830	33,700	38,900
Total	68,000	17,310	215,300	256,600

^a Values are approximate. Actual energy consumption depends upon the particular plant, alloy produced, and product formed.

^b To convert MJ to Mcal, divide by 4.184.

^c Includes forming, baking, and fuel value of anodes.

Some steps in aluminum production are quite energy efficient. Bayer plants make extensive use of heat exchangers to recover heat from material leaving high temperature operations for use in lower temperature operations (see HEAT EXCHANGE TECHNOLOGY). Fluid-bed calciners reduce energy consumption by 30% over the older rotary kiln calciners of alumina. On the other hand, melting and holding furnaces are only about 30% efficient in use of energy. Efficiency has been increased by improved firing practice and in some cases further improved by using heat from stack gases to preheat incoming air. Substituting cryogenic nitrogen for a natural gas-generated inert atmosphere in annealing furnaces saves 30% of the energy required to produce the atmosphere.

Furnaces used to bake anodes for prebake cells use the cooling anodes to preheat combustion air. Hot combustion gases from the baking zone are used to preheat incoming anodes. Using these techniques, about 4.2 MJ/kg (1004 kcal/kg) of anode carbon or only 2520 MJ/t (6.03 × 10⁶ kcal/t) of aluminum is required to produce anodes.

Alternating current is converted to direct current (dc) for the smelting cells by silicon rectifiers. High conversion efficiency (over 99%) and minimum capital costs are achieved when the rectified voltage is 600–900 V dc. Because aluminum smelting cells operate at 4.5–5.0 V, 130 or more cells are connected in series, forming what the industry calls a potline, which may operate at 50–360 kA.

The individual components of smelting-cell voltage and energy are shown in Figure 5. The electrical energy required to decompose alumina $E_1 = 2.233$ V in a cryolite bath 65% saturated with alumina is given by

$$E_1 = (-\Delta G_1/nF) - (RT/nF) \ln a(\text{Al}_2\text{O}_3) \tag{21}$$

where ΔG_1 , the free energy of formation of α -alumina [12252-63-0], is 1280.02 kJ/mol (305.93 kcal/mol), (although the feed to the cell is largely γ - Al_2O_3 , α - Al_2O_3 is the phase in equilibrium with the bath); R is the gas constant (8.314 J/(mol·K)); T is bath temperature (1245 K); $n = 6$ electrons transferred; F is the Faraday constant (96,491 kJ/eq); and $a(\text{Al}_2\text{O}_3)$ is the activity of alumina; a is 0.3 at 65% saturation. Oxygen deposition on the anode is depolarized by carbon, subtracting $E_2 = 1.026$ V given by

$$E_2 = (-\Delta G_2/nF) - (RT \ln F) \ln K \tag{22}$$

where ΔG_2 is the free energy of formation of carbon dioxide and K the oxygen plus carbon reaction equilibrium constant. There is an anode overvoltage slightly over 0.5 V given by

$$E_3 = (RT/\alpha nF) \ln(i/i_o) \tag{23}$$

where i is current density, $n = 2$ electrons per oxygen, and i_o and α are experimental constants typically 50 A/m² and 0.52, respectively. Cathode overvoltage is minimal. Combining E_1 , E_2 , and E_3 gives E_4 the counter electromotive force (CEMF) of the cell of about 1.73 V. Linear extrapolation of cell volts vs current to zero current gives an apparent CEMF about 0.1 V lower because of the change in overvoltage with current. Below 2% alumina concentration, overvoltage becomes significant, the CEMF rises and fluoride is codeposited with oxygen. This causes the bath no longer to wet the anode and a gas envelope to form around it. In order for the current to arc across this poorly conductive layer the voltage must rise (>30 V) and this high voltage, called anode effect, generates some carbon tetrafluoride gas [75-73-0], CF_4 , wastes power, and may overheat the cell. Anode effects can be minimized or eliminated by careful control of alumina additions.

$$E_5 = IL/KA \tag{24}$$

Bath voltage E_5 is about 1.7 V, where I is current, L the anode-to-cathode spacing (4–5 cm), K the electrical conductivity of the bath, 2.0–2.4 (Ωcm)⁻¹, and A the effective bath area. Anode gas bubbles raise the bath's apparent resistivity, increasing its voltage about 0.17 V as indicated by E_6 . Anode voltage E_7 represents the potential drop through the anode, its connecting stub, and the contact between them. It ranges from 0.25 to 0.3 V using prebake anodes and 0.45–0.55 V using Soderberg anodes. Cathode voltage E_8 includes the voltage loss in the lining, collector bars, and the contact between the two. It ranges from 0.35 to 0.55 V. There are also voltage losses in external conductors in the range 0.1–0.2 V, E_9 , that do not contribute heat to the cell.

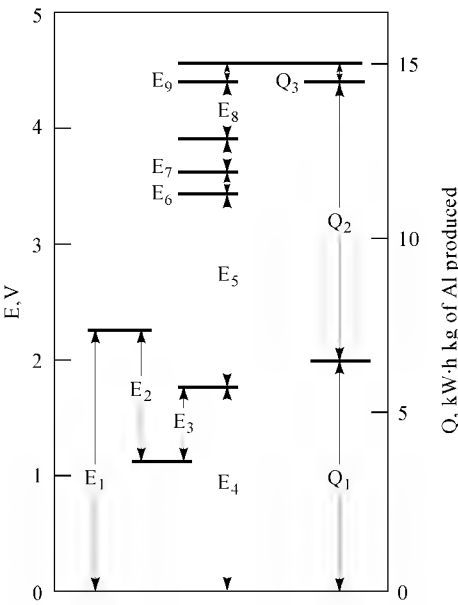


Fig. 5. Energy requirements of the Hall-Héroult cell (23–25). E_1 , decomposition of alumina; E_2 , depolarization by carbon; E_3 , anode overvoltage; E_4 , counter electromotive force; E_5 , bath voltage drop; E_6 , bath bubble voltage; E_7 , anode voltage drop; E_8 , cathode voltage drop; E_9 , external voltage drop; Q_1 , enthalpy to produce aluminum; Q_2 , cell heat losses; Q_3 bus heat loss.

The right side of Figure 5, depicting heat, shows where the electrical power, in volts, is expended. The two scales correspond at 90% current efficiency. Reduction of alumina consumes carbon producing aluminum, carbon dioxide, and carbon monoxide [630-08-0]. Assuming a typical $\text{CO}:\text{CO}_2$ ratio of 0.265, the energy (enthalpy) Q_1 required to reduce alumina (γ - Al_2O_3) using carbon at 970°C is 6.419 kWh/kg of aluminum. Q_1 (19) includes the

energy required to heat the alumina and carbon. The free energy (ΔG) part of the enthalpy (ΔH) required for this reduction is supplied by voltage, $E_1 - E_2$. The heat Q_2 that must be dissipated is 8.12 kWh/kg aluminum. Heating external to this cell is Q_3 , ca 0.53 kWh/kg aluminum. Dividing the productive energy Q_1 by the total electrical energy input $Q_1 + Q_2 + Q_3$ gives an electrical power efficiency of 42.6% for this typical cell.

Carbon consumption also represents energy consumption. Carbon reacting stoichiometrically with alumina to produce aluminum and carbon dioxide would require 0.33 kg carbon per kg aluminum; however, about 0.43 kg carbon per kg aluminum is consumed in the system, making the efficiency of carbon consumption 77%. Both carbon and electrical power can be saved by lowering bath temperature, but decreased alumina solubility and freezing limit this option. Bath additives allow temperature lowering but they also lower alumina solubility. Increasing aluminum fluoride concentration improves current efficiency but also increases the emission of fluoride fumes into the atmosphere. Power can be saved by lowering cell voltage, but when this is accomplished by lowering the anode–cathode spacing, current efficiency is lowered, often nullifying the power saving. Considerable voltage is lost in the anode and cathode. Sumitomo Aluminum licenses technology to achieve 15–20% lower electric power consumption in Soderberg cells by improvements in anode material and design, optimum thermal insulation of the cathode, and use of an automatic alumina feed system. It is difficult to obtain such large gains in prebaked anode cells because they already have higher power efficiency. However, use of cements that improve the electrical contact to the carbon cathode block and substituting semigraphitic carbon for carbon can save 2–5% of electric power.

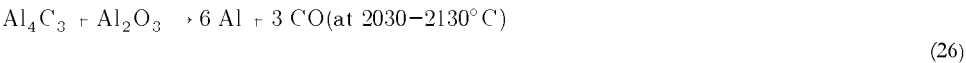
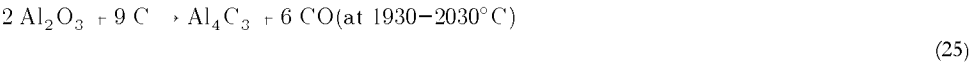
Energy Conservation. The U.S. Department of Energy (DOE) is sponsoring research on inert anodes and refractory hard metal (RHM) composite cathodes. Success in these developments could significantly lower the energy required to reduce alumina. Inert anodes would eliminate the consumption of anode carbon and allow improved sealing of the cell for reduced heat loss and reduced fluoride emission. RHM cathodes would be wetted with a thin film of aluminum which would drain to a sump and provide stable cathodic surface rather than the present aluminum pool that sloshes about owing to electrohydrodynamic effects. The stable cathode should improve current efficiency and also allow closer interelectrode spacing for reduced power consumption. The most promising route to reduced energy requirement, however, is through recycling of scrap aluminum. Recycling scrap requires less than 5% of the energy required to produce new metal. About 60% of aluminum beverage can scrap was recycled in 1990. This should go higher and extend to other aluminum scrap (see RECYCLING).

Comparisons of production energies per metric ton for different metals strongly prejudice the case against light metals. A fairer comparison is energy per unit volume, which more closely approximates the basis for substituting metals. Additionally, the lower energy requirement of recycled metal is often not considered. The energy savings in the application of light metals frequently exceeds the energy for their production. In fact, saving gasoline by substituting aluminum for ferrous materials in automobiles may be one of the nation's lowest cost options for extending fuel supplies (20). At least 10% of the electrical energy generated in the U.S. is lost through heating of transmission and distribution lines. Larger aluminum conductors often give lower lifetime costs (cost of energy lost plus investment costs) and would save energy. Other energy-saving applications include aluminum storm doors and windows, aluminum-pigmented heat-reflecting paints, and aluminum heat exchangers.

Alternative Processes for Aluminum Production. In spite of its industrial dominance, the Hall-H roult process has several inherent disadvantages. The most serious is the large capital investment required resulting from: the multiplicity of units (250–1000 cells in a typical plant), the cost of the Bayer alumina-purification plant, and the cost of the carbon–anode plant (or paste plant for Soderberg anodes). Additionally, Hall-H roult cells require expensive electrical power rather than thermal energy, most producing countries must import alumina or bauxite, and petroleum coke for anodes is in limited supply.

Aluminum can be produced by metallothermic, carbothermic, or electrolytic reduction processes. The earliest commercial process for producing aluminum (1855–1893) was sodiothermic reduction of aluminum halides. Once the Hall-H roult process became commercial, however, sodiothermic reduction was not competitive.

Most attempts at direct carbothermic reduction of alumina have been electrically heated. Low yields of aluminum have been obtained owing to the formation of solid aluminum carbide and aluminum suboxide [12004-36-3], Al_2O_3 , and aluminum vapors that react with carbon monoxide as they leave the furnace (21). However, yields approaching 100% at high energy efficiency can be obtained by staging the reactions as shown below and recovering the volatiles, the back-reaction products, and the heat on incoming reactants (22):



Vaporization and carbide formation can be reduced, however, by adding to the electric furnace a metal (or metal oxide that is subsequently reduced to the metal), such as iron, silicon, copper, or tin to alloy with the aluminum produced and lower its vapor pressure. However this may require a separate purification step to remove the other metal. The greater volume of gas passing through the charge in an aluminum blast furnace generally causes very low yields. Nevertheless, a 33% Al, 42% Fe, 21% Si, 4% others alloy has been successfully produced in a pilot oxygen blast furnace at moderately high yield (23). It is then necessary to extract the aluminum from the alloy in a separate operation. Extraction of pure aluminum from the molten alloy has been accomplished electrolytically by the three-layer process. Attempts have also been made to electro-refine the solid alloy using a low melting chloride electrolyte. Neither method has proved to be economic.

Selective solution of the aluminum from the alloy using a volatile metal, such as mercury, lead, bismuth, cadmium, magnesium, or zinc, has been investigated. After extracting the aluminum from the original alloy into the volatile metal, the volatile metal is distilled, leaving pure aluminum. Neither electrolysis nor volatile metal extraction can extract aluminum from iron aluminide [12004-62-5], FeAl_3 , titanium aluminide [12004-78-3], TiAl_3 , or Al_4C_3 .

A third technique employs monovalent aluminum. By bringing vapors of aluminum fluoride or aluminum chloride into contact with carbothermically reduced aluminum alloy at 1000–1400 C, the following reaction occurs



The monohalide vapors are conveyed to a slightly cooler zone (700–800 C) where the reaction reverses, resulting in the condensation of pure aluminum. The monochloride process was carried to the demonstration plant stage but was abandoned because of corrosion problems (24).

A fourth alloy separation technique is fractional crystallization. If silica is co-reduced with alumina, nearly pure silicon and an aluminum silicon eutectic can be obtained by fractional crystallization. Tin can be removed to low levels in aluminum by fractional crystallization and a carbothermic reduction process using tin to alloy the aluminum produced, followed by fractional crystallization and sodium treatment to obtain pure aluminum, has been developed (25). This method looked very promising in the laboratory, but has not been tested on an industrial scale.

The vapor pressure of aluminum can be lowered by alloying it with aluminum carbide: over 40% aluminum carbide is soluble in aluminum at 2200 C (23). Thus an alloy of aluminum and aluminum carbide was produced at 2400 C by controlling the stoichiometry of the charge (26). When the alloy was tapped from the furnace and allowed to cool slowly, the aluminum carbide crystallized in an open lattice and the interstices filled with pure aluminum. The aluminum was removed by leaching with molten chlorides or by vacuum distillation of the aluminum from the alloy. The aluminum carbide residue was recycled to the arc furnace. This process has been further improved (27), going to three stages to decarbonize the aluminum—two in the hearth and one in an external holding furnace. A liquid aluminum and a slag which was recycled were obtained. The process gave good yields and produced aluminum at less than 11 kWh/kg, but was not developed past the pilot stage.

In 1976 the first section of a new smelting process that required 30% less electric power than the best Hall-H roult cells came on stream. In this process, alumina, carbon, and chlorine reacted to produce aluminum chloride and carbon dioxide. The aluminum chloride was electrolyzed in bipolar electrode cells to produce aluminum and chlorine and the chlorine was recycled to make more aluminum chloride. After six years of operation, the plant

was shut down for economic reasons: repair and maintenance were excessive. The process was designed to use heavy fuel oil (bunker C) as the source of carbon. The chemical reactors never reached design capacity. Increasing their size or number would have been too expensive. The chemical reactor produced a trace of polychlorinated biphenyl which, rather than being destroyed in the cell, continued to accumulate within the system. Its removal and decomposition to environmentally safe products was expensive.

High Purity Aluminum. The Hall-H roult process cannot ensure aluminum purity higher than 99.9  . Techniques such as electrolytic refining and fractional crystallization are required to produce metal of higher purity. Development of an electrolytic refining process was begun in 1901 and made workable by 1919. The Hoopes process is based upon the use of a cell containing three liquid layers, as depicted in Figure 6. Aluminum is electrochemically transported from the bottom alloy layer (anode) through an intermediate electrolyte layer to the high purity top layer (cathode). The bottom phase consists of impure aluminum plus an alloying agent (usually copper) to increase the density above that of the fused salt electrolyte. The composition of the electrolyte is selected to have a density less than the alloy layer but greater than pure aluminum. Electrical connection is made to the alloy through carbon or graphite blocks and graphite is used for the cathode connection. Aluminum is purified because metals more noble than aluminum are not oxidized and remain in the anodic layer. Metals less noble than aluminum are oxidized at the anode, but not reduced at the cathode. Hence impurities accumulate as chlorides or fluorides in the electrolyte.

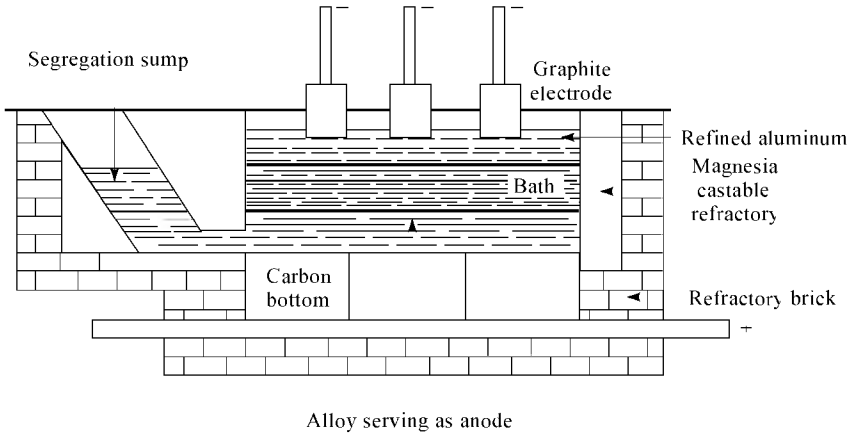


Fig. 6. Cell for the electrolytic refining of aluminum.

This process used an all-fluoride electrolyte, a portion of which was frozen on the carbon sidewalls to prevent short circuiting through the walls. One version of the cell operated at 20,000 A and 950–1000  C. The highest purity aluminum produced was 99.98  . A summary of the cell characteristics is given in Table 9.

Table 9. Electrolytic Purification Processes^a

Characteristic	Hoopes	Pechiney	AIAG Neuhausen
Al purity	<i>Cathode layer</i>		
	99.98��	99.99 �� %	99.99 �� %
	2.29	2.30	2.30
density, g mL	<i>Electrolyte</i>		
composition, ��			
NaF	25–30	17	18
AlF ₃	30–38	23	48
CaF ₂			16
BaF ₂	30–38		18
BaCl ₂		60	
Al ₂ O ₃	0.5–7.0		
density, g mL	2.5	2.7	2.6
resistivity, ��cm	0.3	0.75–0.85	1.1
composition, ��	<i>Anode layer</i>		
Al	75	67	70
Cu	25	33	30
density, g cm ³	2.8	3.14	3.05
cell amperage, A	<i>Operating characteristic</i>		
	20,000	25,000	14,000
	5–7	6.9	5.5–5.3
	0.95	0.40	0.36
	90–98	96–98	92–95
operating temperature, ��C	950–1000	750	740

^a Refs. 14 and 29.

In 1932 the Pechiney Company in France perfected an electrolyte that consists of a chloride–fluoride mixture (Table 9) and melts at 720  C. This allowed low temperature operation (750  C) and the use of a nonconducting magnesia brick lining. Purities as high as 99.995   have been reported. In 1937 the Soci  t   Suisse de l'Aluminum Industrie (AIAG) at Neuhausen patented a low melting (720   C) all-fluoride electrolyte. This electrolyte also allows low temperature operation and the use of a magnesia brick lining. Operating characteristics are similar to the Pechiney process (Table 9).

An important design feature of modern purification cells is the segregation sump pictured in Figure 6 (28). It is normally operated at least 30  C cooler than the main cell and serves as the charging port of the cell. As impurities concentrate on the bottom layer, saturation is reached and crystals preferentially form in the cooler sump where they can be removed. This procedure greatly extends the operating life of the cell and allows use of the process to recover certain types of scrap (29), as well as purifying smelting-grade aluminum. Electrolytic purification, using either of the low melting electrolytes, is a principal source of commercially produced high purity aluminum.

Fractional crystallization processes are also used commercially to produce high purity metal from lower grade aluminum. These processes rely on the

fact that most impurities preferentially concentrate either in the liquid or the solid as aluminum freezes, eg, zone melting (see [ZONE REFINING](#)) (32) where a molten zone is moved along an aluminum bar. Impurities that lower the melting point of aluminum, such as silicon and iron, concentrate in one end of the bar while impurities that raise the melting point, such as titanium and vanadium, concentrate in the other end. After several passes the ends are removed leaving the middle region as the high purity product.

In one process (33) high purity crystals are formed by cooling a molten aluminum surface using air. After the furnace is nearly filled with crystals, the remaining liquid is drained and the crystals remelted to yield the high purity product. Starting with 99.9^o % smelting-grade metal, aluminum of purity higher than 99.995^o % has been produced by fractional crystallization.

Production

The tremendous growth of the aluminum industry as compared to that of other nonferrous metals is shown in Table 10 (30). Aluminum production by country is given in Table 11 (34). The principal markets for aluminum in the United States are containers, packaging, building and construction, and transportation. These markets accounted for 60^o % of industry shipments in 1989. Table 12 (34) shows per capita consumption of aluminum.

Table 10. Annual World Production of Aluminum, Copper, Magnesium, Lead, and Zinc, 10³ t/yr^a

Year	Al	Cu	Mg	Pb	Zn
1900	5.7	449	0.01 ^b	877	479
1950	1516	2791	21.2	1748	1958
1960	4732	4400	93.1	2630	3070
1970	9780	6376	222.8	4003	5097
1980	16043	6083	317.4	5399	6153
1988	17304	5959	338.1	3371	7224

^a Ref. 30.

^b Ref. 31.

Table 11. Annual World Primary Aluminum Production, 10³ t/yr

Country	1960	1970	1975	1980	1985	1988
Africa	44	167	217	437	513	541
Cameroon	44	53	52	43	90	72
Egypt				120	209	179
Ghana		114	143	188	49	118
South Africa			76	87	165	172
North America	2,519	4,570	4,432	5,722	4,782	5,479
Canada	691	963	913	1,068	1,282	1,535
United States	1,828	3,607	3,519	4,654	3,500	3,944
Latin America	19	267	249	821	1,153	1,521
Argentina				133	136	160
Brazil	18	56	138	261	549	874
Mexico				43	43	65
Surinam				55	29	5
Venezuela				328	396	417
East Asia	134	735	1,013	1,174	245	55
Japan	134	735	1,013	1,091	227	35
Korea, Republic of				18	18	20
Taiwan				64		
South Asia	18	162	167	386	903	912
Bahrain				126	176	182
India	18	162	167	185	260	298
Indonesia					217	180
Iran				16	43	40
Turkey				34	54	57
United Arab Emirates				25	153	155
Europe	819	2,015	3,236	3,747	3,630	3,762
Austria	68	90	89	94	94	96
France	235	381	383	432	293	322
Germany, Federal Republic of	169	309	678	731	745	744
Greece				146	125	127
Iceland				73	73	85
Italy	84	147	191	271	224	227
Netherlands				259	251	278
Norway	165	522	591	653	743	840
Spain	29	120	210	386	370	323
Sweden				82	84	98
Switzerland	40	91	80	86	73	72
United Kingdom	29	40	308	374	275	300
Yugoslavia				161	280	250
Oceania	12	207	214	458	1,092	1,350
Australia	12	207	214	303	851	1,150
New Zealand				155	241	200
Other	1,167	1,657	2,562	2,638	3,080	3,684
China, People's Republic	75	127	163	360	410	800
Czechoslovakia				38	32	26
Germany Democratic Republic				60	60	65
Hungary				73	74	75
Korea, Democratic People's Republic				10	10	10
Poland				95	47	48

Romania					241	247	260
USSR	800	1,102	1,497	1,760	2,200	2,400	
<i>Total World</i>	<i>4,732</i>	<i>9,780</i>	<i>12,090</i>	<i>15,383</i>	<i>15,398</i>	<i>17,304</i>	

Table 12. Annual Per Capita Aluminum Consumption, kg/yr

Country	197 8	197 9	198 0	198 1	198 2	198 3	198 4	1985	198 6	198 7	198 8
Argentina ^a	2.2	3.1	2.2	1.8	2.2	2.4	2.5	1.2	2.1	2.5	2.2
Australia ^a	14.7	17.1	17.6	18.8	16.6	15.3	17.5	18.1	17.3	18.8	20.3
Austria ^a	10.8	11.3	12.5	12.0	10.8	11.6	13.1	12.6	14.6	14.2	18.1
Bahrain ^a	6.8	12.5	9.2	6.0	4.9	8.6	10.0	10.8	4.4		
Belgium	8.9	9.2	9.3	7.3	9.3	9.5	12.3	9.6	10.1	7.7	10.4
Brazil ^a	2.6	2.9	3.0	2.4	2.5	2.2	2.2	2.7	3.1	2.9	2.6
Cameroon	1.8	2.1	2.9	1.6	1.6	2.0	2.0	2.2	2.1	1.7	1.2
Canada ^a	16.2	16.8	16.1	16.4	16.9	14.6	19.8	20.4	19.2	22.1	26.8
Denmark	14.6	14.4	12.5	12.4	13.8	13.7	9.1	8.3	9.5	8.6	10.4
Finland	5.4	7.5	6.5	6.4	6.6	5.1	3.4	3.4	5.9	5.3	3.9
France	11.5	12.7	14.3	12.6	13.2	13.1	12.5	12.8	14.1	14.3	16.0
Germany, Federal Republic of ^a	19.5	22.0	22.0	20.3	19.5	21.8	22.3	24.8	25.5	26.2	27.7
Greece	3.9	4.3	5.9	5.9	4.8	4.8	5.2	3.9	5.6	0.6	
Iceland	7.2	9.3	9.9	15.5	10.6	12.8	8.8	7.8	8.2	10.5	12.3
Ireland	4.8	4.9	4.4	4.1	4.0	3.8	5.1	4.5	5.0	5.3	4.4
Italy ^a	11.2	27.7	14.7	12.5	12.3	13.3	13.4	13.7	14.6	16.4	18.0
Japan ^a	18.5	19.5	19.5	17.1	18.6	20.1	18.7	21.5	20.2	21.7	28.0
Korea, Republic of	3.2	3.2	1.9	3.1	3.4	4.2	4.5	4.5			
Mexico ^a	1.9	2.2	2.5	2.9	2.2	1.1	1.6	2.0	1.3	1.3	1.2
Netherlands ^a	10.4	11.8	12.3	9.1	11.3	10.7	12.5	13.7	15.0	14.7	17.5
New Zealand ^a	7.8	8.6	7.8	9.3	7.0	8.3	9.4	10.1	10.2	11.9	10.3
Norway ^a	20.9	24.1	22.7	18.9	22.6	13.3	21.8	20.4	18.4	14.5	21.2
Panama	0.7	0.9	0.9	1.0	0.8	1.5	2.2	0.8	0.8	1.7	1.7
Philippines	0.4	0.7	0.4	0.2	0.4	0.3	0.2	0.1	0.1	0.2	
Portugal	3.9	3.4	3.9	5.0	5.0	4.5	3.1	3.8	4.5		
El Salvador	0.5	0.5	0.2	0.3	0.2	0.5	0.2	0.05	0.2	0.3	0.3
Saudi Arabia	7.9	8.6	11.2	11.4	4.3	20.9	9.0	13.7	5.9	7.3	8.5
Singapore	6.8	9.3	9.2	11.5	10.4	10.4	11.8	11.7	11.6	22.6	20.8
South Africa ^a	2.3	2.6	4.5	4.5	4.1	4.2	4.3	4.2	4.2	4.3	5.2
Spain ^a	5.7	5.8	6.4	5.1	5.5	5.4	4.4	4.5	5.9	6.7	6.9
Sweden ^a	14.8	16.7	15.6	15.5	17.6	18.6	19.9	19.3	20.5	21.4	22.7
Switzerland ^a	13.5	14.2	17.1	15.4	15.1	15.0	18.2	19.1	20.3	18.9	18.9
Taiwan, Republic of China ^a	5.8	6.8	6.1	6.6	6.2	8.9	5.7	7.8			
Turkey	1.1	1.1	1.1	4.0	2.4	2.1	2.5	3.0	3.3	3.3	2.2
United Kingdom	12.1	10.0	9.8	9.4	9.2	9.9	10.7	10.0	10.3	10.9	11.4
United States ^a	29.9	29.9	25.8	25.0	23.1	26.2	26.9	26.6	26.3	27.9	27.5
Venezuela ^a	5.1	6.7	6.9	4.1	6.3	6.4	6.0	4.7	6.7		

^a Adjusted for inventory change.

Economic Aspects

Aluminum prices have historically been more stable than other nonferrous metals. Beginning in the 1970s, however, aluminum prices have fluctuated as shown in Table 13 (30). These fluctuations reflect increased energy costs as well as increased costs of raw materials. Improvements in production processes as well as a rebalancing of demand and supply are expected to stabilize aluminum prices in the future.

Table 13. Aluminum^a Price Averages from 1960 to 1989

Year	Price, \$ kg	Year	Price, \$ kg	Year	Price, \$ kg	Year	Price, \$ kg
1960	0.600	1969	0.599	1978	1.170	1987	1.594
1961	0.561	1970	0.633	1979	1.309	1988	2.427
1962	0.527	1971	0.639	1980	1.534	1989	1.937
1963	0.499	1972	0.583	1981	1.676		
1964	0.523	1973	0.559	1982	1.676		
1965	0.540	1974	0.752	1983	1.712		
1966	0.540	1975	0.877	1984	1.786		
1967	0.551	1976	0.977	1985	1.786		

7		6		5	
196	0.564	197	1.132	198	1.232
8		7		6	

^a Pure, 99.5^o o, ingot aluminum at New York.

Worldwide primary aluminum capacity, Table 14 (35), continues to grow but mostly in countries where there is low cost electric power. Primary capacity in the United States, Table 15, has been reduced from 5,019 thousand metric tons in 1982 to 3,902 thousand metric tons in 1988. The United States and other developed countries are expected to concentrate more on converting raw aluminum into high value added products.

Table 14. World Primary Aluminum Capacity^a

Country	Production, 10 ³ t		Country	Production, 10 ³ t	
	197	198		197	198
	5	9		5	9
Africa		629	Indonesia		225
Cameroon		84	Iran		50
Egypt		175	Turkey		60
Ghana		200	United Arab Emirates		156
South Africa		170	Western Europe		386
					3
North America	562	559	Austria	93	90
	4	0			
Canada	106	162	France	406	298
	6	7			
United States	455	396	Germany, Federal Republic of	755	774
	8	3			
Latin America		191	Greece		145
		9			
Argentina		970	Iceland		88
Mexico		94	Italy	308	206
Surinam		60	Netherlands		266
Venezuela		640	Norway	665	873
Asia		966	Spain	216	337
China, People's Republic		774	Sweden		91
Japan	135	64	Switzerland	95	58
	4				
Korea, Democratic People's Republic		20	United Kingdom	362	300
South Korea		18	Yugoslavia		337
Taiwan		90	Eastern Europe		383
					5
Oceania		142	Czechoslovakia		60
		2			
Australia	230	117	Germany, Democratic Republic		70
		8			
New Zealand		244	Hungary		75
South Asia		130	Poland		60
		1			
Bahrain		200	Romania		250
India		610	USSR	194	332
				1	0

^a Ref. 35.

Table 15. Annual U.S. Primary Aluminum Capacity, 10³ t/yr^a

Company	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Alcoa	1,542.2	1,542.2	1,564.9	1,564.9	1,429.7	1,429.7	1,429.7	1,430.0	1,095.0	1,155.0	1,155.0
Alumax ^b	198.4	198.4	377.1	377.1	385.6	595.1	595.1	599.0	600.0	600.0	600.0
Reynolds	884.5	884.5	884.5	884.5	884.5	884.5	781.1	422.8	422.8	422.8	448.0
Kaiser	656.8	656.8	656.8	656.8	656.8	656.8	526.2	526.2	526.2	383.8	383.8
ARCO Aluminum ^{c,d}	272.2	326.6	326.6	326.6	326.6	326.6	326.6				
Ormet Corp. ^e									244.9	244.9	244.9
Consolidated	319.3	319.3	319.3	319.3	326.8	294.1	292.3	227.2			
Howmet ^b	198.4	198.4	198.4	198.4	207.0						
Noranda	127.0	127.0	127.0	127.0	204.1	204.1	204.1	204.1	204.1	204.1	204.1
Revere	184.3	184.3	184.3	184.3	184.9	184.9	184.9	184.7			
Commonwealth ^f								167.8	167.8		
Alcan ^d								163.3	163.3	163.3	163.3
Columbia Aluminum										167.8	167.8
Columbia Falls ^d								163.3	163.3	163.3	163.3
Vanalco, Inc.										115.0	115.0
National Aluminum	81.6	81.6	81.6	81.6	81.6	86.2	93.9	95.4	95.4	95.4	95.4
Northwest Aluminum ^g									81.6	81.6	81.6
Martin Marietta ^f	190.5	190.5	190.5	190.5	249.5	249.5	249.5	81.6			
Southwire	81.6	81.6	81.6	81.6	81.6	86.2	78.5	79.6	79.6	79.6	79.6

<i>Total</i>	<i>4,737.0</i>	<i>4,791.4</i>	<i>4,992.8</i>	<i>4,992.8</i>	<i>5,018.8</i>	<i>4,997.7</i>	<i>4,761.9</i>	<i>4,345.1</i>	<i>3,844.0</i>	<i>3,876.6</i>	<i>3,901.8</i>
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- ^a Ref. 34.
- ^b Alumas acquired Howmet in 1983.
- ^c Formerly the Anaconda Company (Aluminum Division).
- ^d Alcan Aluminum and Columbia Falls Aluminum acquired 50% each of ARCO Aluminum in 1985.
- ^e Formerly included with Consolidated and Revere.
- ^f Commonwealth acquired 67% of Martin Marietta in 1985.
- ^g Formerly Martin Marietta Goldendale plant.

Analysis

Aluminum is best detected qualitatively by optical emission spectroscopy. Solids can be vaporized directly in a d-c arc and solutions can be dried on a carbon electrode. Alternatively, aluminum can be detected by plasma emission spectroscopy using an inductively coupled argon plasma or a d-c plasma. Atomic absorption using an aluminum hollow cathode lamp is also an unambiguous and sensitive qualitative method for determining aluminum.

Quantitative aluminum determinations in aluminum and aluminum base alloys is rarely done. The aluminum content is generally inferred as the balance after determining alloying additions and tramp elements. When aluminum is present as an alloying component in alternative alloy systems it is commonly determined by some form of spectroscopy (qv): spark source emission, x-ray fluorescence, plasma emission (both inductively coupled and d-c plasmas), or atomic absorption using a nitrous oxide acetylene flame.

The predominant method for the analysis of aluminum-base alloys is spark source emission spectroscopy. Solid metal samples are sparked directly, simultaneously eroding the metal surface, vaporizing the metal, and exciting the atomic vapor to emit light in proportion to the amount of material present. Standard spark emission analytical techniques are described in ASTM E101, E607, E1251 and E716 (36). A wide variety of well-characterized solid reference materials are available from major aluminum producers for instrument calibration.

In addition to the spark emission methods, quantitative analysis directly on solids can be accomplished using x-ray fluorescence, or, after sample dissolution, accurate analyses can be made using plasma emission or atomic absorption spectroscopy (37).

Environmental Considerations

Fluoride emission from aluminum smelting cells has long been an area of great concern (38). One source of fluoride evolution is melt entrained in the gas generated at the anodes. Additionally, sodium tetrafluoroaluminate [13821-15-3], NaAlF₄, has a significant vapor pressure, 190–330 Pa (1.4–2.5 mm Hg), over the melt. The melt vapor pressure increases as melt temperature and aluminum fluoride concentration increase, but decreases as alumina, calcium fluoride, and sodium fluoride concentration increase. Both entrained liquid and NaAlF₄ gas solidify to form fluoride particulates. Moisture entering the melt adsorbed on alumina, and from the hydrogen content of the anodes, results in hydrolysis of AlF₃ in the melt forming hydrogen fluoride (HF) gas. Historically, treatment consisted of passing the exhausted gases through electrostatic precipitators to remove particulates, followed by wet scrubbers to remove HF. This technique has largely been replaced by highly (over 99%) efficient dry scrubbers that catch particulates and sorb HF on alumina (39) that is subsequently fed to the cells. Hence, nearly all the fluoride evolved is fed back into the cell. A monolayer of HF is chemisorbed in the Al₂O₃ and converted to AlF₃ on heating when the alumina is fed to the cell. HF in excess of the monolayer is desorbed and becomes a rapidly increasing circulating load in the system if the alumina used does not have adequate surface area. A surface area of 45 m² g chemisorbs 1.35% HF and is generally adequate.

Hydrocarbon fumes evolved during anode baking are generally disposed of by burning. Additional fuel is required to support combustion because the hydrocarbon concentration is low. In some plants these products are now absorbed in a fluid bed of alumina for burning in a concentrated form. This treatment also catches the fluoride evolved during anode baking.

Handling of alumina and coke presents dusting problems. Hoods and exhaust systems collect the dust, which is then separated from the exhaust air either by cyclones, electrostatic precipitators, filter bags, or a combination of these methods, and recycled to the process (see AIR POLLUTION CONTROL METHODS).

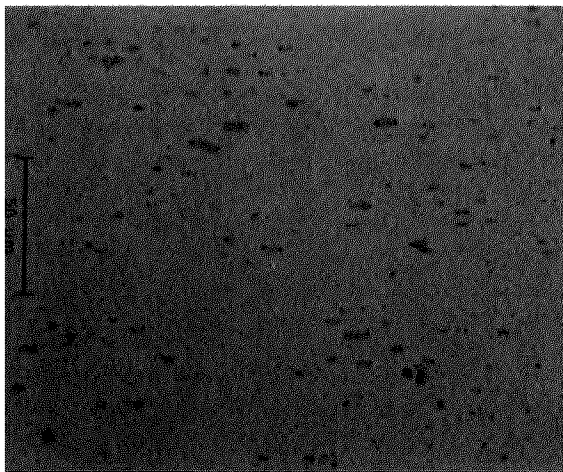
Chlorine fluxing of aluminum to remove hydrogen and undesirable metallic impurities has largely been supplanted by fumeless fluxing procedures, which generally employ a low vapor pressure melt of alkali chlorides containing a small amount of aluminum chloride as the active ingredient.

The linings of aluminum reduction cells must be replaced periodically. These spent linings represent the largest volume of waste associated with the smelting process. Because they contain fluorides and cyanide, they must be either stored under roof or buried in landfills lined with impervious materials to prevent leaching and contamination of the environment. The large volumes involved make these procedures costly and research is being directed toward destroying the cyanide and recovering valuable components from the lining. Some potential uses for recoverables are as a flux in the steel industry, in making rock wool, as supplemented fuel for cement manufacture, and as fuel in fluidized-bed boilers.

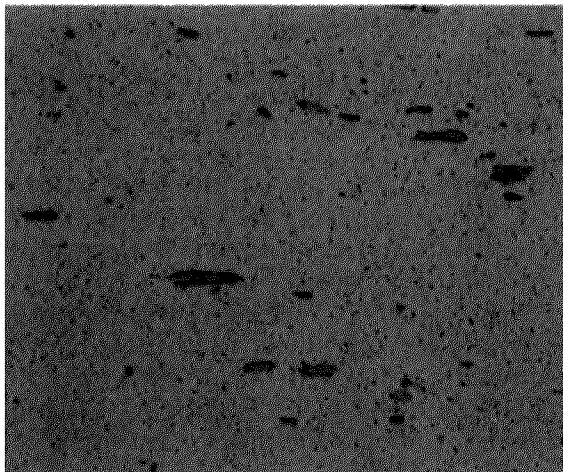
Aluminum Alloys

Aluminum obtained by electrolysis of cryolite baths contains iron [7439-89-6] and silicon [7440-21-3] as impurities. Iron content may vary from 0.05 to 0.4% and silicon from 0.05 to 0.15% depending on the raw materials and the age and condition of the reduction cell. Primary aluminum metal also contains small, usually not to exceed 0.05% in total, amounts of many other elements. Some of these trace impurities are Cu, Mn, Ni, Zn, V, Na, Ti, Mg, and Ga, most of which are present in quantities substantially below 100 ppm.

Many of the properties of aluminum alloy products depend on metallurgical structure which is controlled both by the chemical composition and by processing (40). In addition to features such as voids, inclusions, grains, subgrains, dislocations, and vacancies which are present in virtually all metallic products, the structure of aluminum alloys is characterized by three types of intermetallic particles. Aluminum metallurgists refer to these as constituent particles, dispersoid particles, and precipitate particles. Constituent particles are formed during solidification generally as a byproduct of a divorced eutectic reaction and range in size in the final product from about 1–20 micrometers, Figure 7a. These particles, present in all aluminum alloys, play a role in grain-size control and negatively affect toughness of high strength alloy products. Dispersoids and precipitates both form by a solid-state reaction. The particles known as dispersoids characteristically form during thermal treatment of an ingot by precipitation of a solid solution which exceeds maximum solid solubility because of nonequilibrium conditions during ingot solidification. Dispersoids, about 10–200 nm in the largest dimension, are present in most aluminum alloy products. See Figures 7b and 8. Their primary function is to control grain size, grain orientation (texture), and degree of recrystallization. Particles classified as precipitates form during heat treatment of the final mill product by precipitation from a supersaturated solid solution that does not exceed the maximum equilibrium solid solubility. In the final product, their size may range from disks a few atoms thick by a few nm in diameter up to needlelike or platelike particles which may exceed 1 micrometer in the largest dimension (Fig. 9). Precipitates may confer high strength. The nature of the constituent, dispersoid, and precipitate particles depends strongly on the phase diagrams of the particular alloy.



(a)



(b)

Fig. 7. Alloy 3004 sheet. (a) Al (Fe, Mn) and Al₁₂(Fe, Mn) Si constituent particles. Magnification is $\times 500$. (b) Etched to reveal the Al (Fe, Mn) and Al₁₂(Fe, Mn) dispersoids. Magnification is $\times 1000$.

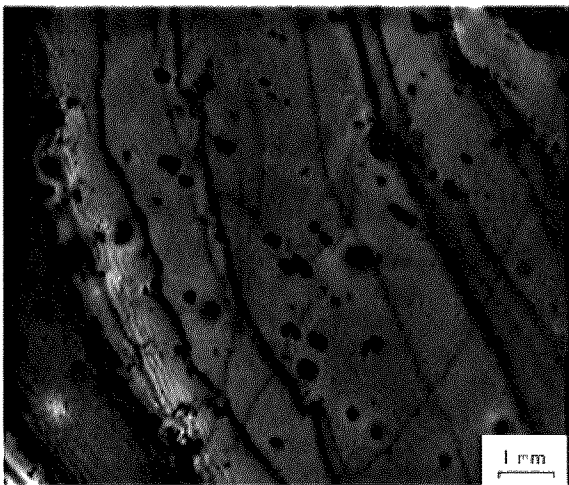


Fig. 8. Transmission electron micrograph showing the Al₁₂(Fe, Mn)₃Si and Al (Fe, Mn) dispersoid particles in alloy 3004 sheet.



Fig. 9. Transmission electron micrograph at 40,000 magnification showing S'-phase precipitates in Al-Cu-Mg alloy sheet aged 12 h at 100°C.

Binary Alloys. Aluminum-rich binary phase diagrams show three types of reaction between liquid alloy, aluminum solid solution, and other phases: eutectic, peritectic, and monotectic. Table 16 gives representative data for reactions in the systems Al-M. Diagrams are shown in Figures 10–19. Compilations of phase diagrams may be found in reference 41.

Table 16. Phase Transformations in Binary Aluminum Alloys

Al-M system	Reaction		Solubility of M %		Other phase
	Type	Temperature, °C	Solid	Liquid	
Al-Si	eutectic	577	1.65	12.60	Si
Al-Cr	peritectic	651	0.77	0.41	Cr ₃ Al ₇
Al-Pb	monotectic	326.8			Pb

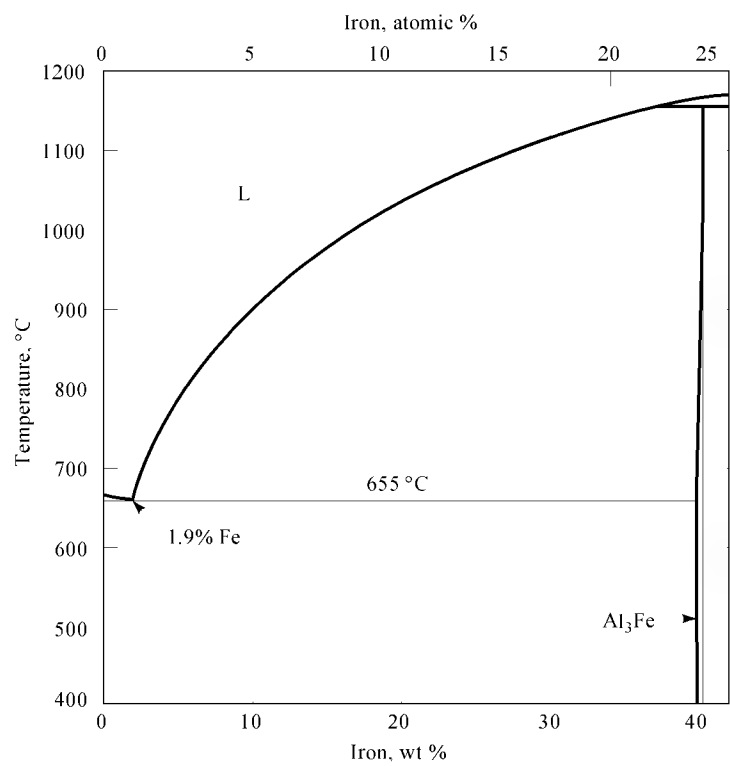


Fig. 10. Al-Fe phase diagram, where L is liquid. Drawing by J. Murray.

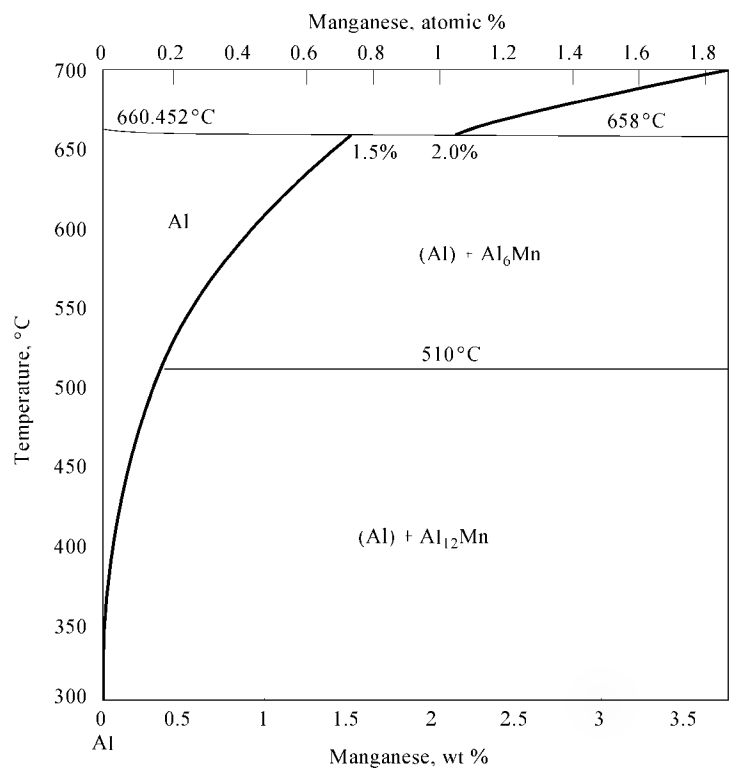


Fig. 11. Al-Mn phase diagram, where L is liquid. Drawing by J. Murray.

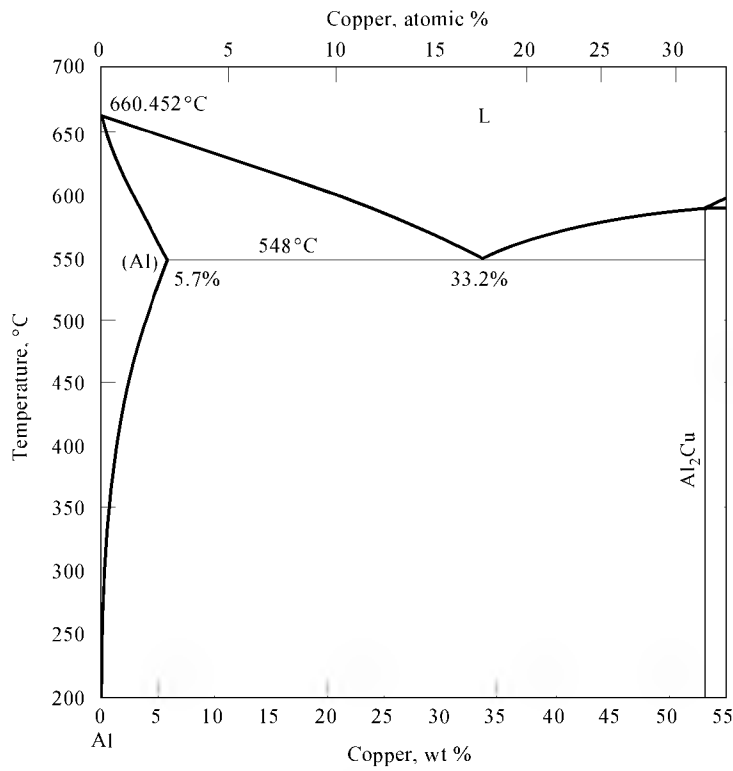


Fig. 12. Al–Cu phase diagram, where L is liquid. Drawing by J. Murray.

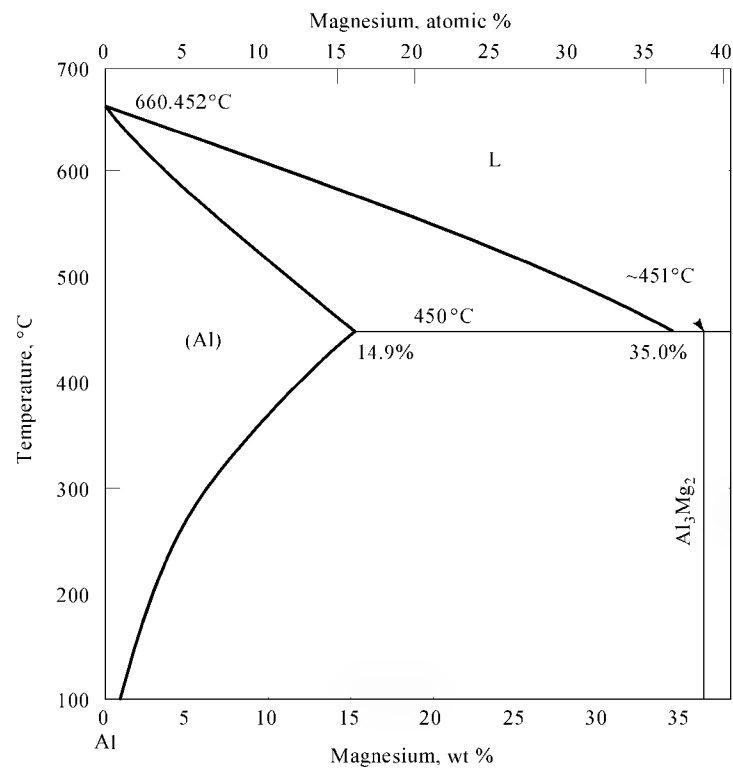


Fig. 13. Al–Mg phase diagram, where L is liquid. Drawing by J. Murray.

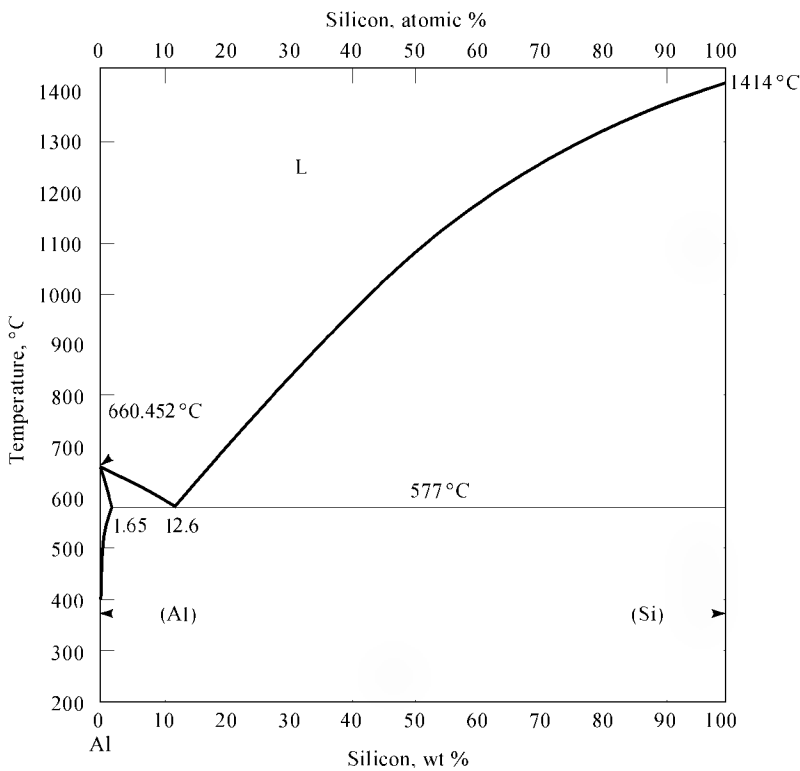


Fig. 14. Al-Si phase diagram, where L is liquid. Drawing by J. Murray.

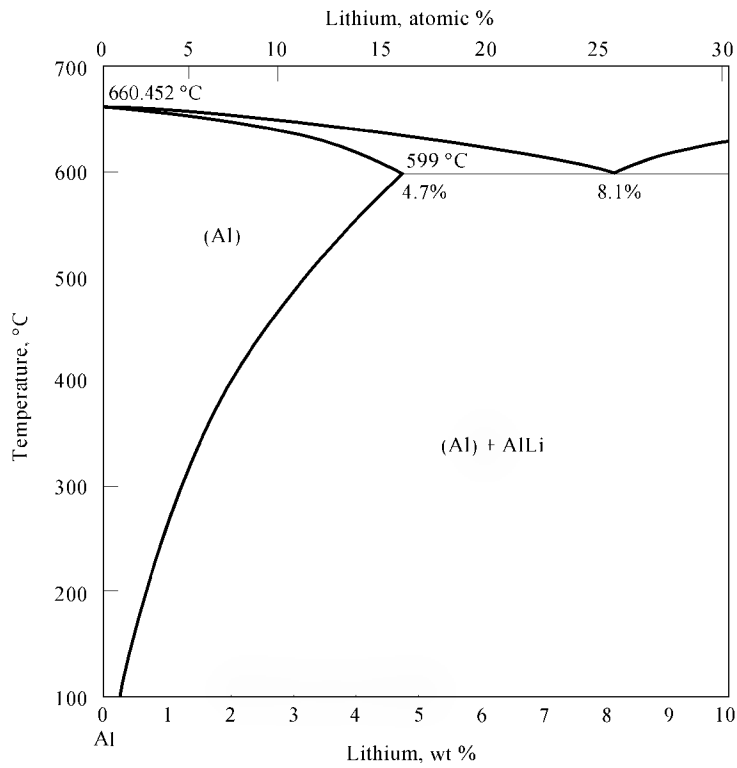


Fig. 15. Al-Li phase diagram. Drawing by J. Murray.

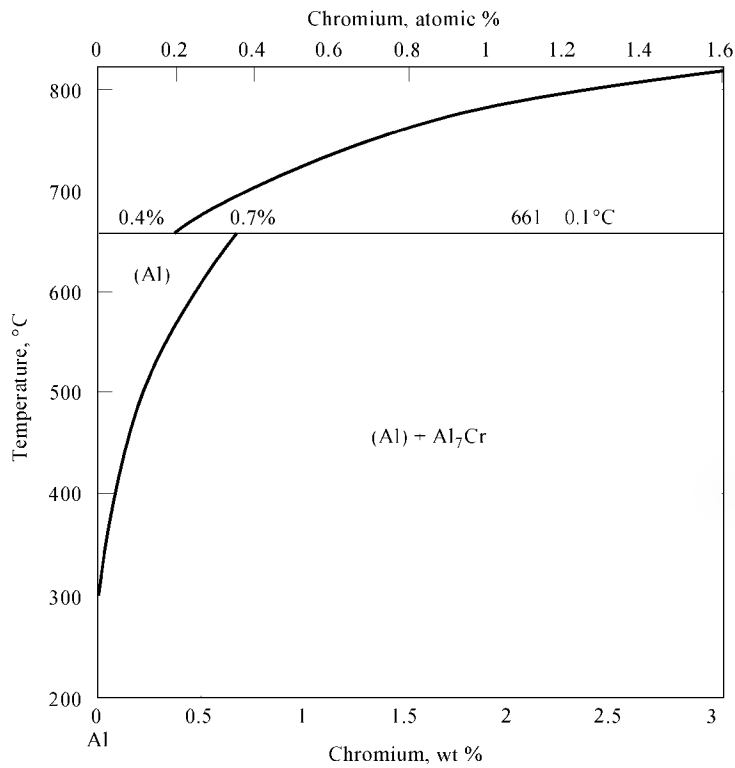


Fig. 16. Al–Cr phase diagram. Drawing by J. Murray.

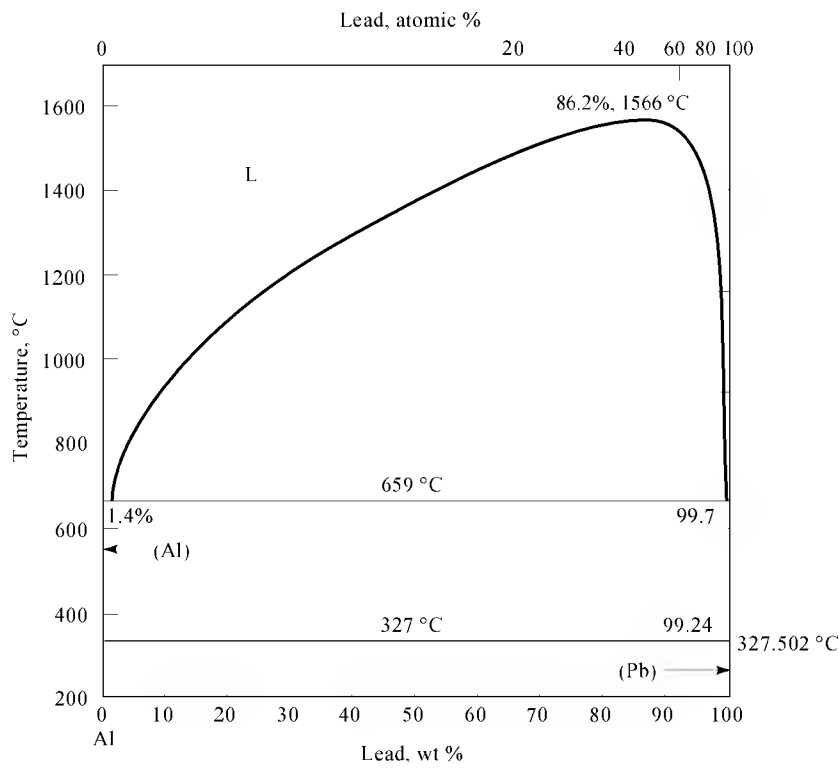


Fig. 17. Al–Pb phase diagram, where L is liquid. Drawing by J. Murray.

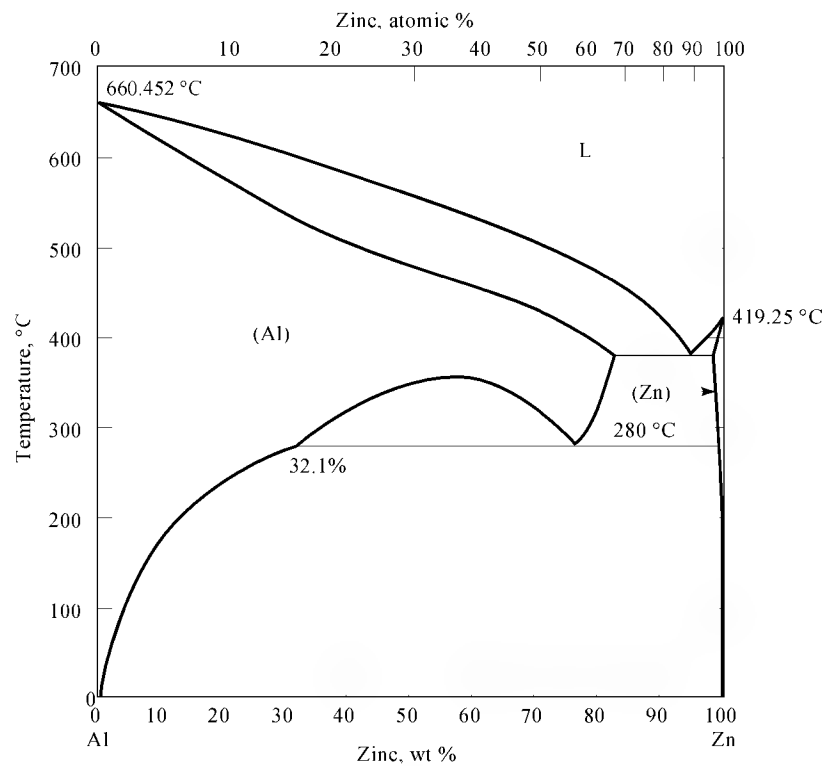


Fig. 18. Al–Zn phase diagram, where L is liquid. Drawing by J. Murray.

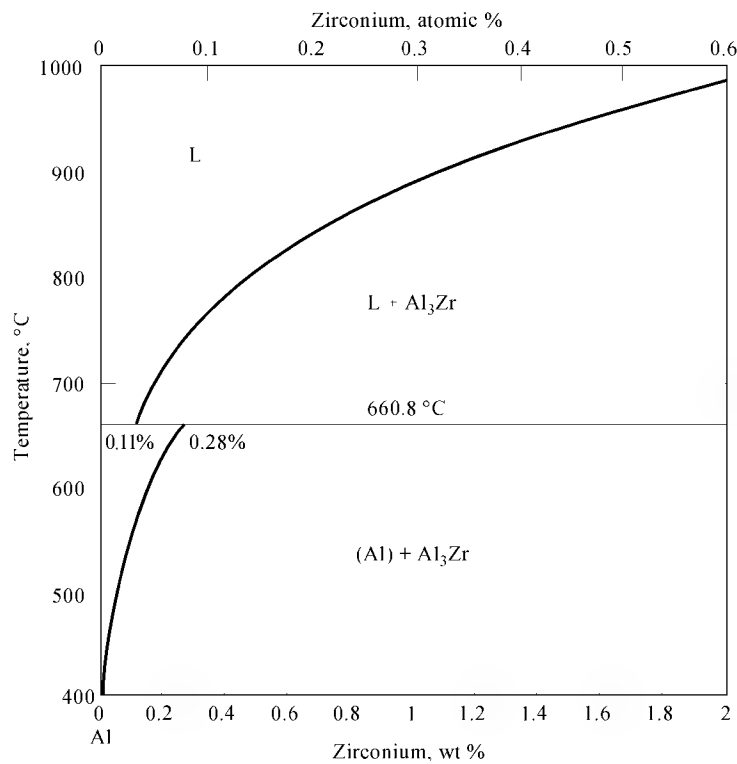


Fig. 19. Al–Zr phase diagram, where L is liquid. Drawing by J. Murray.

Al–Fe. The Al–Fe system (Fig. 10), is important because virtually all commercial aluminum alloys contain some iron [7439-89-6], Fe. The system has a eutectic at 1.9% Fe, but solid solubility of only 0.05% Fe. Consider an alloy containing 0.3% Fe. During solidification, most of the Fe remains in the liquid phase until a eutectic of solid solution plus Al₃Fe constituent particles freezes. Alternatively, constituents of the metastable Al–Fe phase [12005-28-6] may form during solidification. These transform to equilibrium Al₃Fe by heating above 500°C. If the solidification rate is rapid enough, more than 0.05% Fe remains in supersaturated solid solution. This excess amount can precipitate as Al₃Fe dispersoids during subsequent thermal treatment. In more complex alloys, such as Al–Fe–Si, Al–Fe–Mn, and Al–Cu–Fe, most of the iron is contained in constituent particles formed by eutectic decomposition. In all cases the maximum solid solubility of iron in aluminum is 0.05% or less.

Al–Mn. The Al–Mn system (Fig. 11), the basis for the oldest yet most widely used aluminum alloys, is characterized by a eutectic at 1.95% Mn and 658°C. Maximum solid solubility is 1.76% manganese [7439-96-5], Mn, and the intermetallic phase in aluminum-rich alloys is Al₁₂Mn [12043-69-5]. The Al₁₂Mn phase [12446-45-6] is difficult to nucleate in binary Al–Mn alloys, but Al₁₂(Mn,Cr) forms readily in the Al–Mn–Cr ternary alloy. Most of the manganese added to commercial alloys is usually retained in supersaturated solution in the ingot. Commercial alloys based on the Al–Mn system always contain some iron and silicon, and in the presence of these elements manganese precipitates as dispersoids which may be Al₃(Fe,Mn) or Al₁₂(Fe,Mn)₃Si. The dispersoid particles provide a modicum of dispersion strengthening, increase the degree of strain hardening, refine the recrystallized grain structure and influence its crystallographic orientation, and minimize strain localization during plastic deformation.

Al–Cu. Many structural aluminum alloys contain significant amounts of copper [7440-50-8], Cu. There is a eutectic in the Al–Cu system at 33.2% Cu and 548°C, but the important feature (Fig. 12) is the maximum solubility of 5.7% Cu at 548°C which decreases drastically at lower temperatures.

This decreasing solubility with decreasing temperature is necessary for the phenomenon known as age hardening or precipitation strengthening. Consider an alloy containing 4% Cu. During solidification, it separates into a solid solution of copper in aluminum and a liquid containing copper in aluminum until a temperature of 548°C is reached. Then, the remaining liquid freezes as a solid solution of 5.7% Cu in Al plus a eutectic of this solid solution and Al₂Cu constituent particles. The alloy product may be subsequently heated in the solid-state above about 425°C to dissolve the Al₂Cu constituents (solution heat treatment). Rapid cooling to room temperature (quenching) retains the Cu in supersaturated solution. This unstable solution decomposes at room temperature (natural aging) by the formation of clusters of Cu atoms (G–P or Guinier–Preston zones) on preferred crystallographic planes. The G–P zones strengthen the alloy product by resisting the passage of dislocations. Heating to 100–200°C (artificial aging or elevated temperature precipitation treatment) provides enough energy for the formation of metastable forms of Al₂Cu precipitates (θ' or θ'') which provide even more strengthening. Thermal treatment at 250°C and higher (annealing) converts the metastable precipitates to the equilibrium Al₂Cu precipitates (θ), and the product softens.

Al–Mg. Almost every commercial precipitation strengthened aluminum alloy contains magnesium as an alloying element. The Al–Mg system (Fig. 13) has a eutectic at 35% magnesium [7439-95-4], Mg, and 451°C. Maximum solid solubility is 14.9% Mg, and solubility decreases to about 0.8% Mg at room temperature. Despite this decreased solubility, precipitation strengthening by the metastable β' -phase precursor to the equilibrium β -phase Al₃Mg₂ precipitates is observed only at very high magnesium levels. Commercial alloy products based on the Al–Mg system are strengthened by the effect of the magnesium in solid solution (solid solution hardening). Strength is enhanced by cold-working the products (strain-hardening). Strength levels are not as high as in most precipitation strengthened alloys, but the products have good ductility and corrosion resistance.

Al–Si. Al–Si alloys (Fig. 14) possess high fluidity and castability and are consequently used for weld wire, brazing, and as casting alloys. The range of silicon [7440-21-3], Si, is about 5 to 20% in commercial casting alloys. This system has a eutectic at 12.6% Si and 577°C; maximum solid solubility of Si is 1.65%. The constituent which forms during eutectic decomposition is essentially pure Si. Hypereutectic alloys are used for engine blocks because the hard Si particles are wear-resistant. The Si particles, which form during solidification, are coarse and acicular. Micro additions of sodium [7440-23-5], Na, antimony [7440-36-0], Sb, and strontium [7440-24-6], Sr, modify the faceted structure of primary silicon particles in hypereutectic alloys to spherulitic and the flake structure of eutectic silicon to a finer fibrous morphology.

Al–Li. Alloys containing about two to three percent lithium [7439-93-2], Li, (Fig. 15) received much attention in the 1980s because of their low density and high elastic modulus. Each weight percent of lithium in aluminum alloys decreases density by about three percent and increases elastic modulus by about six percent. The system is characterized by a eutectic reaction at 8.1% Li at 579°C. The maximum solid solubility is 4.7% Li. The strengthening precipitate in binary Al–Li alloys is metastable Al₃Li [12359-85-2], δ' , having the cubic Ll₂ crystal structure, and the equilibrium precipitate is complex cubic Al–Li [12042-37-4], δ . The nature of the phase relationships involving δ' has been the subject of much discussion. Portions of the metastable phase boundaries have not yet been agreed upon.

Al–Cr. Although no commercial alloys are based on this system, chromium [7440-47-3], Cr, is an ingredient of several complex and commercially significant alloys (Fig. 16). The Cr is added for control of grain structure. The Al–Cr system has a peritectic portion at 661°C where solid solubility is 0.7% Cr and liquid solubility is 0.4% Cr. Freezing of binary alloys containing >0.4% Cr produces coarse primary crystals (metallic inclusions) of Al₇Cr [12005-37-7] which may adversely affect mechanical properties. In complex alloys, the liquid solubility can be reduced such that formation of primary Al₇Cr crystals may occur at significantly lower Cr contents.

Al–Pb. Both lead [7439-92-1], Pb, and bismuth [7440-69-9], Bi, which form similar systems (Fig. 17), are added to aluminum alloys to promote machinability by providing particles to act as chip breakers. The Al–Pb system has a monotectic reaction in which Al-rich liquid freezes partially to solid aluminum plus a Pb-rich liquid. This Pb-rich liquid does not freeze until the temperature has fallen to the eutectic temperature of 327°C. Solid solubility of lead in aluminum is negligible; the products contain small spherical particles of lead which melt if they are heated above 327°C.

Al–Zn. Aluminum-rich binary alloys (Fig. 18) are not age hardenable to any commercial significance, and zinc [7440-66-6], Zn, additions do not significantly increase the ability of aluminum to strain harden. Al–Zn alloys find commercial use as sacrificial claddings on high strength Al–Cu–Mg–Zn aircraft alloy sheet. The eutectoid composition near 78% Zn has found use as a superplastic sheet alloy.

Al–Zr. This system (Fig. 19) has a peritectic reaction at 660.8°C at which solubility is 0.28% zirconium [7440-67-7], Zr, solid and 0.11% Zr liquid. The equilibrium phase on the aluminum-rich end of the phase diagram is tetragonal Al₃Zr [12004-83-0], β . Coarse primary particles of β -phase have a tendency to form during solidification when the zirconium content is much above 0.12%. A metastable form of Al₃Zr having a cubic Ll₂ structure, β' , is formed when supersaturated zirconium precipitates as a dispersoid. Although this phase is nonequilibrium, it is extremely resistant to transformation to the equilibrium β -phase.

Ternary Alloys. Almost all commercial alloys are of ternary or higher complexity. Alloy type is defined by the nature of the principal alloying additions, and phase reactions in several classes of alloys can be described by reference to ternary phase diagrams. Minor alloying additions may have a powerful influence on properties of the product because of the influence on the morphology and distribution of constituents, dispersoids, and precipitates. Phase diagrams, which represent equilibrium, may not be indicative of these effects.

Al–Fe–Si. Iron and silicon, present in primary aluminum, may also be added to produce enriched alloys for specific purposes. The equilibrium phase fields in the Al–Fe–Si system are shown in Figure 20 and Table 17. The intermetallic phases have a limited range of composition when in equilibrium with the aluminum solid solution. The amount of iron in solid solution in the matrix is small, so almost all of the iron is in the intermetallic compounds. At low silicon contents the iron is present as Al₃Fe except for about 0.01% Fe in solid solution. As silicon content increases, the ternary intermetallic compound Al₁₂Fe₃Si, α -(Al–Fe–Si), appears. At higher silicon contents Al₉Fe₂Si₂, β -(Al–Fe–Si), appears in which a higher amount of silicon is combined with iron. The positions of the phase fields move to lower silicon content with decreasing temperature.

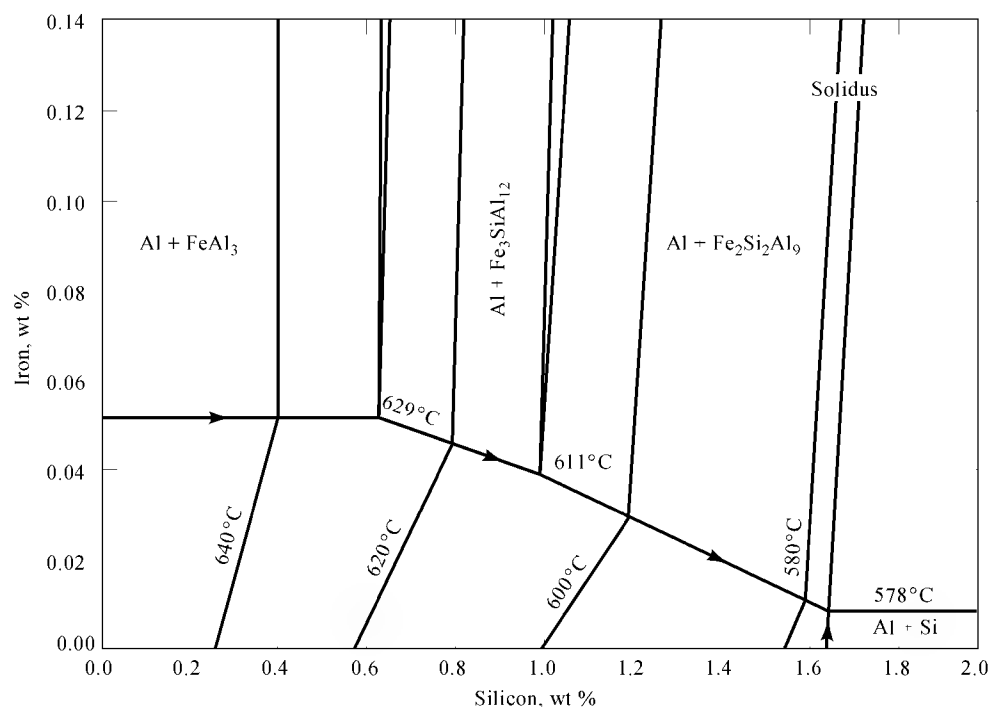


Fig. 20. Solidus for aluminum-rich Al–Fe–Si alloys.

Table 17. Intermetallic Phases in Al–Fe–Si Alloys

Designation	Formula	CAS Registry Number	Fe, %	Si, %
	Al ₃ Fe	[12004-62-5]	41	negligible
α-(Al–Fe–Si)	Al ₁₂ Fe ₃ Si	[12397-58-9]	32	5.5
β-(Al–Fe–Si)	Al ₉ Fe ₂ Si ₂	[12397-57-8]	27	14
	Si	[7440-21-3]	negligible	~100

The phases present in products can differ from those predicted from equilibrium diagrams. Nonequilibrium metastable phases form at solidification rates experienced in commercial ingots. Because of the low rate of diffusion of iron in aluminum, equilibrium conditions can only be established by long heat treatments and are very slowly approached at temperatures below about 550°C. Small additions of other elements, particularly manganese, can also modify the phase relations.

Al–Mg–Si. An important class of commercial alloys is based on the Al–Mg–Si system because of its precipitation hardening capabilities and good corrosion resistance. The precipitation hardening results from precipitation of a metastable precursor of magnesium silicide [22831-39-6], Mg₂Si, from solid solution. The phase relations are as shown in Figure 21. At low magnesium contents the alloys may contain silicon as a second phase. As magnesium increases, the ternary phase field Al–Mg₂Si–Si is entered, and at higher magnesium contents the phase field Al–Mg₂Si. The solubility of Mg₂Si decreases at higher magnesium contents. Heat treatment at high temperatures can put as much as 1.8% Mg₂Si into solid solution, and cooling at a sufficient rate can retain it therein. The cooling rate required depends on the amount of Mg₂Si dissolved. Compositions that have magnesium and silicon in the exact ratio to form Mg₂Si are not widely employed commercially, because alloys containing silicon in excess of that required to form Mg₂Si develop higher strength. Silicon, however, has a tendency to precipitate on grain boundaries. Consequently, excess-silicon alloy products must be quenched at a higher rate to prevent brittle intergranular fracture.

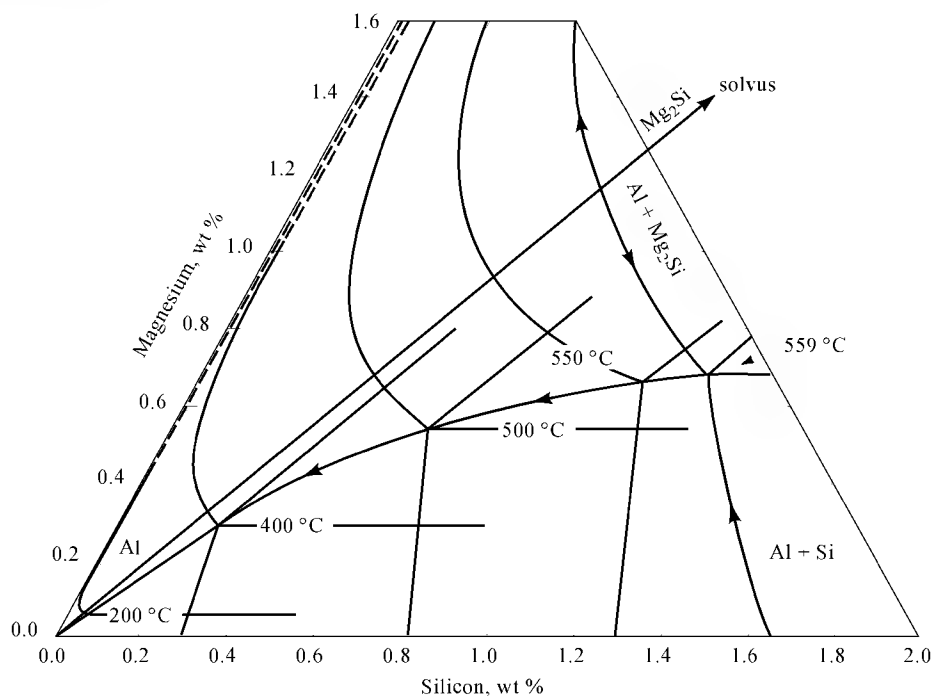


Fig. 21. Solvus for aluminum-rich Al–Mg–Si alloys.

Al–Mg–Mn. The basis for the alloys used as bodies, ends, and tabs of the cans used for beer and carbonated beverages is the Al–Mg–Mn alloy system. It is also used in other applications that exploit the excellent weldability and corrosion resistance. These alloys have the unique ability to be highly strain hardened yet retain a high degree of ductility. Some of the manganese combines with the iron to form Al (Fe,Mn) or Al₁₂(Fe,Mn)₃Si constituent particles during solidification, but most remains in supersaturated solid solution until it precipitates as Al (Fe,Mn) or Al₁₂(Fe,Mn)₃Si dispersoids during ingot thermal treatment. No ternary Al–Mg–Mn phases are present in commercial alloys; mechanical properties reflect the enhanced strain hardening characteristics of the matrix with magnesium in solution and the effects of the Mn-bearing dispersoids in stabilizing the deformation substructure.

Most alloys contain no more than 5% Mg and because of the slow precipitation kinetics of Al₃Mg₂ at these levels, the magnesium is easily retained in solution during processing. Natural aging is insignificant at these low magnesium levels, but with levels of 4% Mg or more, small amounts of β may precipitate at grain boundaries after long times, and this may cause susceptibility to intergranular corrosion. Special thermal treatments (tempers) have been developed to prevent this.

Al–Cu–Mg. The first precipitation hardenable alloy was an Al–Cu–Mg alloy. There is a ternary eutectic at 508°C, and there are nine binary and five ternary intermetallic phases. For aluminum-rich alloys, only four phases are encountered in addition to the aluminum solid solution (Table 18). Several commercial alloys are based on the age hardening characteristics of the metastable precursors of θ or S-phase, principally θ' or S'. Hardening by T- and β-phases is not very effective. Alloys of greatest age hardenability have compositions near the Cu:Mg ratio of the S-phase. Additions of about 0.12% Mg to alloys containing as much as 6% Cu, however, significantly increase strength by refining the θ' precipitate.

Table 18. Intermetallic Phases in Al–Cu–Mg Alloys

Designation	Formula	CAS Registry Number	Cu, %	Mg, %
θ	Al ₂ Cu	[12004-15-8]	54	negligible
S	Al ₂ CuMg	[12004-18-1]	46	17
T	Al CuMg ₄	[12253-80-4]	25	28
β	Al ₃ Mg ₂	[12004-68-1]	negligible	38

Solid-state reactions in these alloys can be understood with reference to Figures 22 and 23. Heat-treatable Al–Cu–Mg alloys are solution treated above the solvus temperatures for S-phase or θ-phase and quenched. At age hardening temperatures the solvus curves are at very low copper and magnesium contents, and appreciable supersaturation is achieved. As magnesium increases above the ratio in S-phase the amount of this phase that can be formed decreases, so the amount of age hardening decreases. The excess magnesium contributes to solid solution strengthening. Excess copper is restricted by the solubility of θ-phase. The precursors to both θ- and S-phases are heterogeneously nucleated during elevated temperature precipitation heat treatments. Cold-working after quenching and prior to artificial aging increases the density of dislocations that nucleate precipitation, thus refining the precipitate structure and increasing strength.

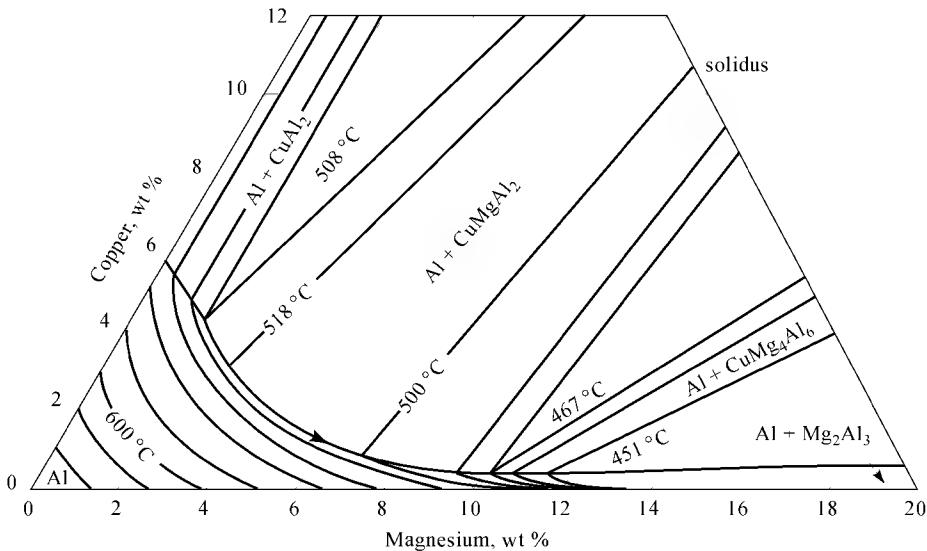


Fig. 22. Solidus for aluminum-rich Al–Cu–Mg alloys.

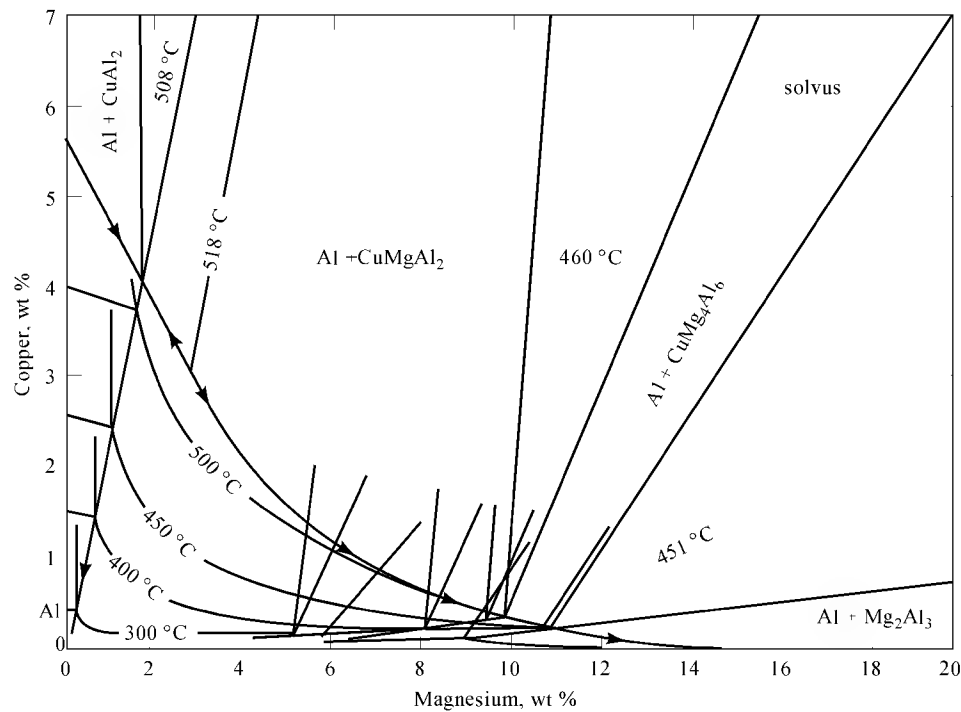


Fig. 23. Solvus for aluminum-rich Al–Cu–Mg alloys.

Al–Mg–Zn. Although neither aluminum-rich binary Al–Zn nor Al–Mg alloys are precipitation hardenable, the ternary system is a source of alloys strengthened in this manner. The intermetallic phases encountered in aluminum-rich alloys are shown in Table 19. Alloy compositions are selected for precipitation of an M- or v-phase precursor because T-phase is less effective as a strengthener. Commercially important alloys always contain more zinc than magnesium to provide attractive combinations of strength, extrudability, and weldability. As a generality, resistance to stress-corrosion cracking increases as the Zn:Mg ratio increases.

Table 19. Intermetallic Phases in Al–Mg–Zn Alloys

Designation	Formula	CAS Registry Number	Mg, %	Zn, %
M or η	MgZn ₂	[12032-47-2]	17	79
T	Al ₂ Mg ₃ Zn ₃	[12004-33-0]	30–20	25–70
β	Al ₃ Mg ₂	[12004-68-1]	38	negligible

The Al–Mg–Zn solidus in Figure 24 illustrates the high solid solubility of both magnesium and zinc. Melting temperatures of the eutectics are lower than in the Al–Mg–Si and Al–Cu–Mg systems. Solid-state reactions can be understood with reference to Figure 25. Substantial amounts of magnesium and zinc can be dissolved well below melting temperatures, and appreciable supersaturation and age hardening can be achieved.

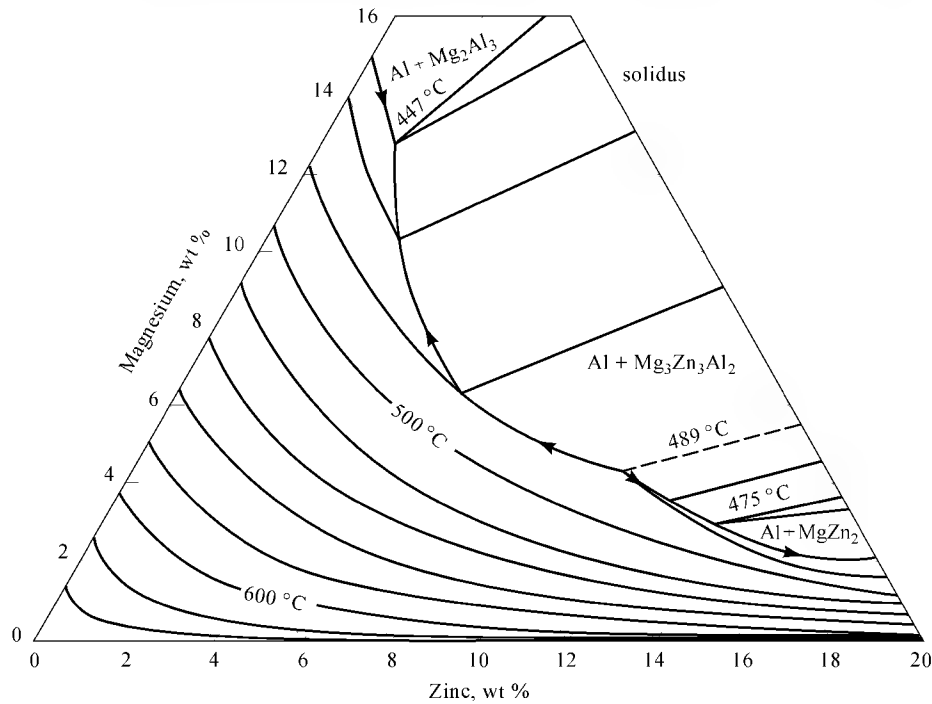


Fig. 24. Solidus for aluminum-rich Al–Zn–Mg alloys.

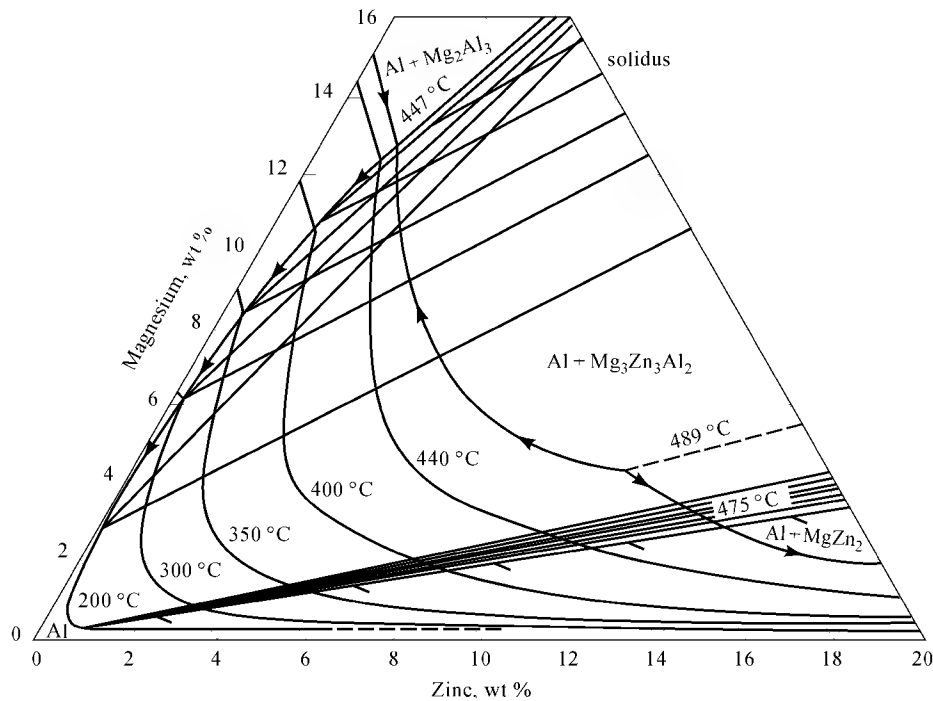


Fig. 25. Solvus for aluminum-rich Al-Zn-Mg alloys.

Al-Cu-Li. Although the addition of Cu to Al-Li alloys increases density, the boost in strength more than offsets the density increase so that Al-Cu-Li alloy products develop higher specific strengths (strength density) than do binary Al-Li alloy products. Furthermore, the fracture toughness and corrosion resistance of products manufactured from Al-Cu-Li alloys are higher than these properties in binary Al-Li alloy products. The phases in equilibrium at 327–350°C are presented in Figure 26 (42). Designations for equilibrium and metastable phases in Al-Cu-Li alloys and their crystal structures are presented in Table 20 in order of increasing lithium content of the phase. The strengthening precipitates in most Al-Cu-Li alloys that have commercial significance are δ' and T_1 . The T_2 -phase decreases toughness when it precipitates on grain boundaries.

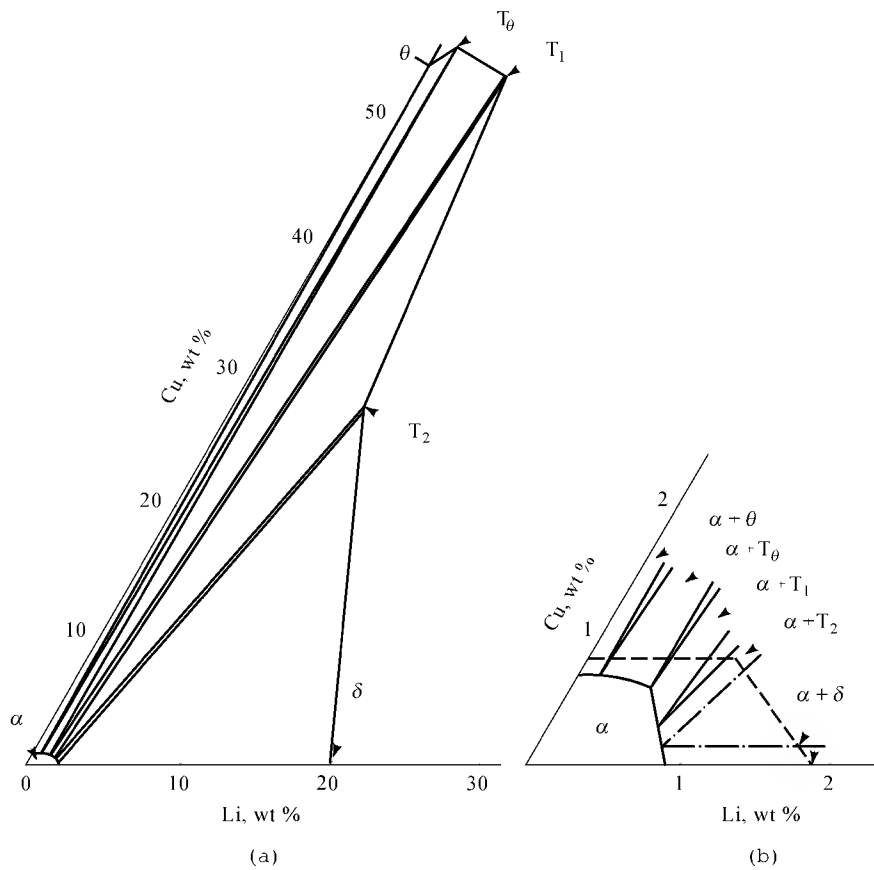


Fig. 26. Isothermal section of Al-Cu-Li system at 350 °C (adapted from ref. 43); **a**, isothermal section; **b**, limits of solid solubility for α -phase. Solid lines correspond to proposed limits for 327 °C (44); dashed lines correspond to 350 °C section.

Table 20. Equilibrium and Metastable Phases in Al-Cu-Li Alloys

Designation	Formula	Crystal structure
θ	Al_2Cu	tetragonal
θ'	Al-Cu	tetragonal
θ''	Al-Cu	tetragonal

Ω	Al–Cu	tetragonal
T_B	Al Cu ₄ Li	CaF ₂
T_1	Al ₂ CuLi	hexagonal
R	Al ₅ CuLi ₃	Im3
T_2	Al CuLi ₃	icosohedral
T_2	Al CuLi ₃	rhombohedral
δ'	Al ₃ Li	L1 ₂
δ	AlLi	B32

Al–Li–Mg. In aluminum-rich alloys the ternary phase, T, sometimes designated as Al₂LiMg, is encountered in addition to AlLi (δ), Al₃Mg₂ (β), and Al₁₂Mg₁₇ [12254-22-7] (γ), Figure 27. Assessment of the composition of the T-phase indicates that it contains 15.5 atomic % Mg and 32 atomic % Li. The high solubility of magnesium is unaffected by lithium, and no metastable phase in addition to Al₃Li (δ') is formed. Alloys in this system are solid solution strengthened by magnesium and age harden by precipitation of δ' .

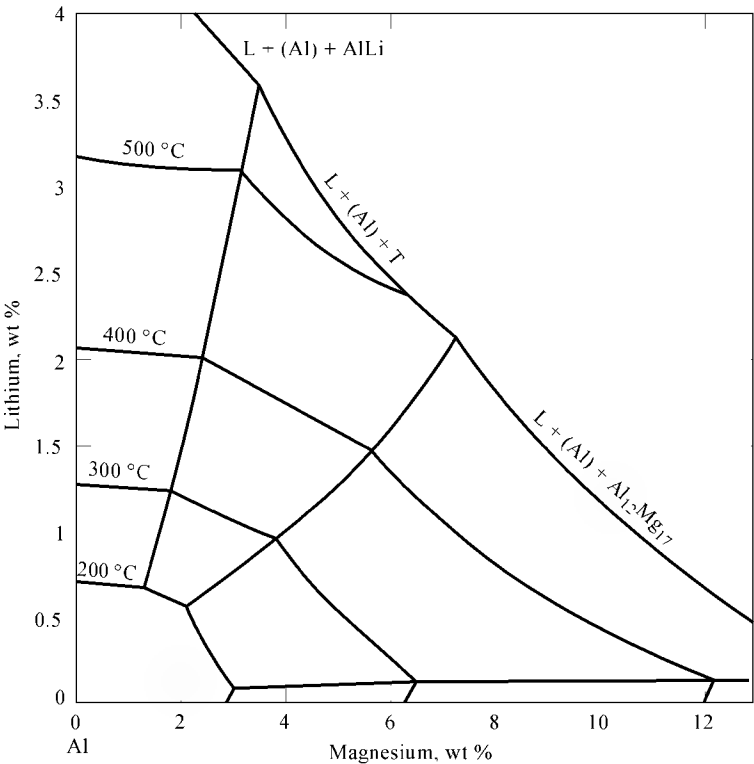


Fig. 27. Projection of solvus surface of Al–Li–Mg system, where L is liquid and T is temperature.

Quaternary and Higher Alloys. Further additions to commercial aluminum alloys usually are made either to modify the metastable strengthening precipitates or to produce dispersoids.

Modifications to Precipitates. Silicon is sometimes added to Al–Cu–Mg alloys to help nucleate S' precipitates without the need for cold work prior to the elevated temperature aging treatments. Additions of elements such as tin [7440-31-5], Sn, cadmium [7440-43-9], Cd, and indium [7440-74-6], In, to Al–Cu alloys serve a similar purpose for θ' precipitates. Copper is often added to Al–Mg–Si alloys in the range of about 0.25% to 1.0% Cu to modify the metastable precursor to Mg₂Si. The copper additions provide a substantial strength increase. When the copper addition is high, the quaternary Al₄CuMg₅Si₄ Q-phase must be considered and dissolved during solution heat treatment.

The highest strength aluminum alloy products are based on the Al–Cu–Mg–Zn system and all are strengthened by precursors to the η -phase. Copper and aluminum can substitute for zinc in MgZn₇, so η -phase may be represented as Mg(Al,Cu,Zn). No quaternary phases are a factor in aluminum-rich Al–Cu–Mg–Zn alloys, but Al₂CuMg, S-phase, may be present in higher solute alloys. The isopleth in Figure 28 for alloys in the ratio of 1.6% Cu, 2.5% Mg, and 5.6% Zn illustrates that the S-phase solvus is always higher than that for η -phase for such alloys. The addition of copper to Al–Mg–Zn alloys above about 0.25% Cu increases strength and reduces the weldability and resistance to general corrosion of products, whereas additions above about 1.5% Cu significantly increase strength and resistance to stress-corrosion cracking.

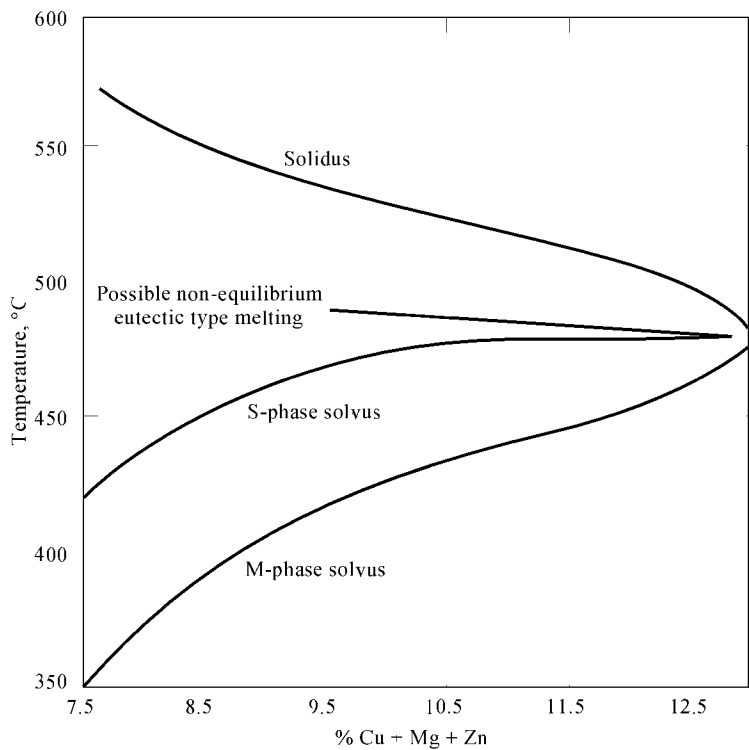


Fig. 28. Isopleth in Al–Cu–Mg–Zn system where the appropriate ratio is Cu:Mg:Zn = 1:1.4:3.3.

Courtesy of E. DoPos.

Several of the Al–Li alloys developed in the 1980s contain both magnesium and copper. No quaternary Al–Cu–Li–Mg phase has been found in the alloys. The S'-phase in addition to δ' and T₁ provides precipitation hardening.

When combined with magnesium, silver [7440-22-4], Ag, has found commercial use as an alloying element in several aluminum alloys for specialized applications. It was added to an Al–Cu–Mg–Zn forging alloy to increase the resistance to stress-corrosion cracking and to an Al–Cu–Mg casting alloy to increase strength. In the late 1980s, combined Ag and Mg additions were shown to increase strength of an Al–Cu alloy (45). Additions of lithium to this basic composition further increased strength (46). The effect of the combined usage of Ag and Mg was attributed to promoting the precipitation of a phase designated Ω that was believed to contain Mg and Ag atoms, but has recently been identified in a binary Al–Cu alloy (47).

Dispersoid Formers. The three elements commonly added to precipitation hardenable alloys to form dispersoids are manganese, chromium, and zirconium. The amounts customarily used (0.5% Mn, 0.2% Cr, and 0.1% Zr) remain in supersaturated solid solution during ingot casting and precipitate as dispersoids during thermal treatment of the ingot. These dispersoids serve to minimize recrystallization during solution heat treatment of products such as plate, forgings, and extrusions which are hot-worked, and to maintain a fine recrystallized grain size in sheet and tubing which is cold-worked.

The manganese in commercial Al–Cu–Mg alloys precipitates as Al₂₀Cu₂Mn₃ [12355-72-5] dispersoid particles. These dispersoids also help strengthen the products because, during quenching, they promote the formation of dislocations that serve as sites for heterogeneous nucleation during artificial aging. The chromium in commercial Al–Cu–Mg–Zn alloys precipitates as Al₁₂Mg₂Cr dispersoids. These particles are more effective than Al₂₀Cu₂Mn₃ dispersoids in controlling recrystallization and in providing fine grain size in cold-worked products. They do not contribute to age hardening, but serve to nucleate η-phase particles heterogeneously during a slow quench, decreasing the strength of slowly quenched products because the solute is unavailable for controlled precipitation during artificial aging treatments. The zirconium in commercial Al–Cu–Mg–Zn, Al–Cu–Li, and Al–Cu–Mg alloys precipitates as metastable Al₃Zr, β', dispersoids. Products which contain β'-phase dispersoids are not as quench sensitive as those which contain Al₁₂Mg₂Cr. Alloys in the Al–Mg–Si system may contain either manganese, chromium, or zirconium. Some Al–Mg–Zn alloys contain both chromium and manganese, and at least one contains all three dispersoid forming elements.

Foundry Alloys and Their Characteristics. Unalloyed aluminum does not have either mechanical properties or casting characteristics suitable for general foundry use yet both can be greatly improved by the addition of other elements. The most common addition is silicon which enhances fluidity, increases resistance to hot-cracking, and improves pressure tightness. Because binary Al–Si alloys have relatively low strengths and ductility, other elements such as copper and magnesium are added to obtain higher strengths through heat treatment. The compositions of representative foundry alloys are shown in Table 21, and typical mechanical properties are presented in Table 22.

Table 21. Compositions of Aluminum Foundry Alloys

Aluminum Association designation	Casting process ^a	Alloying elements, %				Applications
		Si	Cu	Mg	Others ^b	
208.0	S	3.0	4.0			general purpose
213.0	P	2.0	7.0			cylinder heads, timing gears
242.0	S,P		4.0	1.5	2.0 Ni	cylinder heads, pistons
295.0	S	1.1	4.5			general purpose
B295.0	P	2.5	4.5			general purpose
308.0	P	5.5	4.5			general purpose
319.0	S,P	6.0	3.0			engine parts, piano plates

A332.0	P	12.0	1.5	1.0	2.5 Ni	pistons, sheaves
F332.0	P	9.5	3.0	1.0		pistons, elevated temperatures
333.0	P	9.0	3.5	0.3		engine parts, meter housings
355.0	S,P	5.0	1.3	0.5		general: high strength, pressure tightness
356.0	S,P	7.0		0.3		intricate castings: good strength, ductility
360.0	D	9.5		0.5	2.0 Fe max	marine parts, general purpose
380.0	D	8.5	3.5		2.5 Fe max	general purpose
A413.0	D	12.0				large intricate parts
443.0	D	5.3			2.0 Fe max	carburetors, fittings, cooking utensils
B443.0	S,P	5.3			0.8 Fe max	general purpose
514.0	S			4.0		hardware, tire molds, cooking utensils
520.0	S			10.0		aircraft fittings
A712.0	S		0.5	0.7	6.5 Zn	general purpose

^a S, sand cast; P, permanent mold cast; D, pressure die cast.

^b Aluminum and impurities constitute remainder.

Table 22. Mechanical Properties of Aluminum Foundry Alloys

Alloy and temper	Tensile strength, MPa ^a	Yield strength, MPa ^a	Elongation, %	Brinell hardness
<i>Sand castings</i>				
208.0–F	145	95	2.5	55
242.0–T21	185	125	1	70
242.0–T77	205	160	2	75
295.0–T4	220	110	9	60
295.0–T6	250	165	5	75
319.0–F	185	125	2	70
319.0–T6	250	165	2	80
355.0–T6	240	170	3	80
356.0–T6	225	165	3	70
B443.0–F	130	55	8	40
514.0–F	170	85	9	50
520.0–T4	330	180	16	75
A712.0–T5	240	170	5	75
<i>Permanent mold castings</i>				
242.0–T61	325	290	0.5	110
308.0–F	195	110	2	70
319.0–F	235	130	2.5	85
319.0–T6	275	185	3	95
F332.0–T5	250	195	1	105
355.0–T6	290	185	4	90
356.0–T6	260	185	5	80
B443.0–F	160	60	10	45
<i>Die castings</i>				
360.0	305	170	3	75
380.0	315	160	3	80
A413.0	290	130	3	80
443.0	225	95	9	50

^a To convert MPa to psi, multiply by 145.

The alloys are identified by a series of three-digit numbers where the first digit indicates the alloy group as shown. The aluminum is at least 99% pure.

First digit	1	2	3	4	5	7	8	9
Element	Al	Cu	Si–Cu–Mg	Si	Mg	Zn	Sn	Other

In addition to these elements, foundry alloys may contain a small amount of titanium [7440-32-6], Ti, for grain refinement, as well as small additions of manganese, chromium, or nickel [7440-02-0], Ni. A high strength Al–Cu–Mg alloy for aircraft use contains silver for added strength by modifying the precipitate phase. Alloys intended for pressure die casting may have high iron contents to resist welding to the dies. Lower grades of the same alloys may be used in sand casting and permanent mold castings with some benefits to mechanical properties. Castings are produced in an F temper (as-cast) and a T temper (heat treated) where higher strengths or other special characteristics are desired.

Die castings produced in a cavity which has been evacuated contain significantly less porosity and hence, are more ductile. Such castings were produced on an experimental basis in the 1980s. In the 1990s, this process is expected to compete with components either fabricated from sheet metal or

forged.

Wrought Alloys and Their Characteristics. Alloys for the production of wrought products are selected for fabricability as well as their physical, chemical, and mechanical properties. Usually, these alloys are less highly alloyed than those for foundry use and contain less iron and silicon. A series of alloys based on the eutectic Al–Fe–Si composition, however, has been developed to provide good combinations of strength and formability in thin sheet products. The compositions of some of the more common alloys are shown in Table 23. The alloys are identified by four-digit numbers, where the value of the first digit identifies the alloy type and principal alloying addition. The aluminum is at least 99⁰ % pure.

First digit	1	2	3	4	5	6	7	8
Element	Al	Cu	Mn	Si	Mg	Mg + Si	Zn	Other

In addition to these principal alloying elements, which provide solid solution strengthening and/or precipitation strengthening, wrought alloys may contain small amounts of titanium and boron [7440-42-8], B, for control of ingot grain size, and ancillary additions of chromium, manganese, and zirconium to provide dispersoids. All commercial alloys also contain iron and silicon.

Table 23. Compositions of Wrought Aluminum Alloys

Aluminum Association designation	Alloy elements, %						Others ^a	Applications
	Si	Cu	Mn	Mg	Cr	Zn		
1100		0.12					1.0Si + Fe max	sheet metal work, pots, pans
1350							0.5 max	electrical conductor
2008	0.7	0.9		0.4				automotive sheet
2014	0.8	4.4	0.8	0.5				aircraft structures, truck frames
2024		4.4	0.6	1.5				aircraft structures, truck wheels
2036		2.6	0.25	0.45				automotive sheet
2090		2.7					2.2 Li, 0.12 Zr	aircraft structure
2091		2.2		1.5			2.0 Li, 0.08 Zr	aircraft structure
2219		6.3	0.3				0.1 V, 0.18 Zr, 0.06 Ti	aerospace structures, welded
2519		5.9	0.3	0.2			0.1 V, 0.18 Zr	armor and aerospace structures, welded
3003		0.12	1.1					general purpose, cooking utensils
3004			1.1	1.0				general purpose, can sheet
3105			0.6	0.5				building products
5052				2.5	0.25			general purpose
5083			0.7	4.4	0.15			unfired pressure vessels
5182			0.35	4.5				can sheet, automotive sheet
5252				2.5				automotive bright trim
6009	0.8	0.33	0.33	0.05				automotive sheet
6010	1.0	0.33	0.33	0.8				automotive sheet
6013	0.8	0.8	0.5	1.0				armor and aerospace structures, welded
6061	0.6	0.25		1.0	0.20			general purpose, structures
6063	0.4			0.7				general purpose, extrusions
6201	0.7			0.8				electrical conductor
7005			0.45	1.4	0.13	4.5	0.14 Zr	truck bodies, railroad cars
7075		1.6		2.5	0.25	5.6		aircraft structures
7150		2.2		2.3		6.4	0.12 Zr	aerospace structures
8090		1.3		0.9			2.4 Li, 0.12 Zr	aerospace structures

^a Aluminum and impurities constitute remainder.

Mechanical properties of wrought aluminum alloy mill products depend on temper as well as on chemical composition. The letter O following the alloy designation indicates a final annealing operation to achieve lowest strength and highest ductility. The letter H indicates that the product is in a strain-hardened condition or temper as a result of cold rolling, drawing, or other types of working. The first digit following the H indicates whether the product received some thermal treatment after cold working; the second digit implies property level. The letter T signifies a heat treatment to obtain solute precipitation and hardening. The numbers following the T further define the condition of the product by indicating the type of thermal or working operation employed in producing the material.

Mechanical properties also depend on product form and test direction because the manufacturing operations used to produce the mill products may significantly affect the final crystallographic texture and extent of mechanical fibering. For example, the longitudinal yield strength of alloy 7075–T6 rod produced by axisymmetric extrusion may be as much as 140 MPa (20,000 psi) higher than that of 7075–T6 sheet. The typical long-transverse mechanical properties of some wrought aluminum alloys in the form of sheet or plate are presented in Table 24.

Table 24. Long Transverse Properties of Wrought Aluminum Alloy Products

Alloy and temper	Tensile strength, MPa ^a	Yield strength, MPa ^a	Elongation, %	Brinell hardness	Elastic modulus, MPa ^a × 10 ³
1100–O	90	35	35	23	69

1100–H14	125	115	9	32	69
1100–H18	165	150	5	44	69
1350–O	85	30			69
1350–H19	185	165			69
2008–T4	250	125	28		69
2014–T6	485	415	13	135	73
2024–T3	485	345	18	120	73
2024–T81	485	450	7	125	73
2036–T4	345	200	24		69
2090–T83	560	520	7		80
2091–T84	420	315	18		79
2219–T62	415	290	10	110	73
2219–T81	455	350	10	123	73
2519–T87	500	450	11		78
3003–O	110	40	30	28	69
3003–H14	150	145	8	40	69
3003–H18	200	185	4	55	69
3004–O	180	70	20	45	69
3004–H34	240	200	9	63	69
3004–H38	285	250	5	77	69
3105–O	115	55	24		69
3105–H25	180	160	8		69
5052–O	195	90	25	47	70
5052–H34	260	215	10	68	70
5052–H38	290	255	7	77	70
5083–O	290	145	22	65	71
5083–H321	315	225	16	82	71
5182–O	270	130	23	64	71
6009–T4	235	130	24	63	69
6010–T4	295	185	23	67	69
6013–T6	395	350	11		69
6061–O	125	55	25	30	69
6061–T4	240	145	22	65	69
6061–T6	310	275	12	95	69
6063–T6	240	215	12	73	69
7005–T53	395	345	15	105	70
7075–T6	570	505	11	150	72
7075–T76	525	450	11		72
7075–T73	505	415	11		72
7150–T77	600	565	10		71
8090–T81	460	360	7		81

^a To convert MPa to psi, multiply by 145.

THERMAL TREATMENTS

Aluminum alloys are subjected during manufacture to a variety of thermal treatments that range from heating to assist fabrication, to heating for control of final properties. Although the natural oxide film on aluminum provides good protection against surface oxidation and deterioration during such treatments, controlled atmospheres are sometimes employed for products requiring minimum surface oxide such as foil and sheet for reflectors. The atmosphere may be nitrogen or burned producer gas that is dried prior to use in the furnace. The introduction of sulfur compounds into furnace atmospheres should be avoided because in the presence of moisture sulfur compounds tend to break down the protective aluminum oxide film permitting further oxidation to occur. Nascent hydrogen is a product of such a reaction and may diffuse into the metal, forming voids or blisters, especially in the high strength Al–Cu–Mg or Al–Cu–Mg–Zn alloys. Such problems can be minimized by using low dew point atmospheres, eliminating sulfur compounds, and paying careful attention to recommended times and temperatures of heat treatment. Additional protection can be obtained by adding small quantities of boron trifluoride [7637-07-2], BF₃, or one of several fluoroborate compounds to the furnace atmospheres. These fluorides tend to form protective films that resist breakdown by moisture and sulfur compounds.

Homogenization. Ingots are usually preheated prior to rolling, forging, or extrusion to increase workability. The process is commonly referred to as homogenization because chemical segregation of the major alloying elements that are completely soluble in the solid-state is reduced. In addition, however, supersaturation of elements such as manganese, chromium, and zirconium is relieved during the preheat operation, so these elements become more segregated when they precipitate as dispersoids. Also during the homogenization treatment, metastable compounds may transform into the more stable equilibrium form.

Incipient melting is usually avoided during preheating, but homogenization treatments are often close to eutectic or solidus temperatures, so care must be taken. Preheat practices known as superpreheating were developed in the 1920s and 1930s to increase productivity of extrusion and to provide a fine equiaxial grain structure. Incipient melting was deliberately produced followed by slow, controlled cooling. Procedures where incipient melting is deliberately produced to modify the structure and increase certain mechanical properties were published in the 1980s (48).

Annealing. The resistance to further deformation of aluminum alloy products at elevated temperatures reaches a steady value after a modest strain when the rate of formation of fresh dislocations is balanced by the rate of annihilation. This process is known as dynamic recovery. During deformation processing by hot rolling, the metal temperature has a tendency to decrease. When this happens the rate of dynamic recovery decreases, so the resistance to further deformation increases because the dislocation density increases. In the rolling of sheet to thicknesses below about 4 mm, the final 25 to 50% reduction is usually done cold to provide close dimensional control. In-process annealing is employed to decrease the dislocation density thereby increasing the plasticity of the hot-rolled metal prior to cold rolling. This thermal process also modifies the crystallographic texture, a very important consideration in producing products requiring control of anisotropy. During cold rolling, the dislocation density progressively increases with increasing strain, so for the thinnest sheet or foil, more than one in-process anneal may be employed. The temperatures employed for annealing are usually in the range of 350–400°C.

Annealing is also employed as a final mill operation to produce a material having high formability for subsequent customer shaping or forming

operations. For precipitation hardenable alloys, the cooling rate must be controlled so that the equilibrium phases precipitate as coarse, nonstrengthening particles. Some tempers of strain-hardenable alloy products are produced by partial annealing or recovery treatments to provide attractive combinations of strength and formability. Highly cold-worked products are heated for combinations of time and temperature sufficient to provide enough energy to rearrange and eliminate some of the dislocations introduced during cold working but insufficient to allow the product to recrystallize by the motion of high angle grain boundaries.

Solution Heat Treatment. Solution heat treatment is the first stage of a series of operations to achieve precipitation hardening. The product is heated to a high temperature to dissolve as many soluble particles as practicable. Times for adequate dissolution depend on the size of the particles to be dissolved. Thick castings generally require many hours because the particles are a combination of products of eutectic decomposition and of precipitates which form and coarsen during the slow cool of the casting. Thin sheet may require less than a minute provided that the process was controlled so that the precipitate particles did not coarsen during fabrication. Heating is usually performed in an electrical resistance furnace, but molten salt is used for higher heating rates to produce fine grain size in sheet. Transverse flux induction heating was introduced in the 1980s to provide high heating rates without the problems associated with salt run-off. Much sheet is solution heat treated in a continuous web, fed from a coil into a horizontal furnace.

Quenching. After solution treatment, the product is generally cooled to room temperature at such a rate to retain essentially all of the solute in solution. The central portions of thicker products cannot be cooled at a sufficient rate to prevent extensive precipitation in some alloys. Moreover, some forgings and castings are deliberately cooled slowly to minimize distortion and residual stress produced by differential cooling in different portions of the products. Cold water, either by immersion or by sprays, is the most commonly used cooling medium. Hot water or a solution of a polymer in cold water is used when the highest rates are not desired. Dilute Al–Mg–Si and Al–Mg–Zn extrusions can be effectively solution heat treated by the extrusion process; therefore, they may be quenched at the extrusion press by either air or water.

Precipitation Heat Treatment. The supersaturated solution produced by the quench from the solution temperature is unstable, and the alloys tend to approach equilibrium by precipitation of solute. Because the activation energies required to form equilibrium precipitate phases are higher than those to form metastable phases, the solid solution decomposes to form G-P zones at room temperature (natural aging). Metastable precursors to the equilibrium phases are formed at the temperatures employed for commercial precipitation heat treatments (artificial aging).

Natural Aging (Room Temperature Precipitation Heat Treatments). Certain alloys are capable of developing commercially useful properties when the products are allowed to age at room temperature. In general, the properties of 2XXX alloy products stabilize after about a week, and those of 6XXX alloy products attain about 90% of their peak properties after the same time period (Table 25). Products of these alloys are referred to as being in the T4 temper after about one week natural aging. For several Al–Cu–Mg alloys, cold working a few percent before natural aging is complete significantly increases strength relative to material in a T4 temper. The T3 temper designation is used to describe such products. In contrast to the behavior of 2XXX and 6XXX alloy products, properties of 7XXX alloy products continue to change at a logarithmic rate for decades. Consequently, naturally aged 7XXX alloy products are not used for commercial applications. The W temper designation accompanied by a time is used to describe 7XXX alloy products in naturally aged conditions.

Table 25. Age Hardening of Aluminum Alloys 6061 and 2024 at Room Temperature after Heat Treatment and Quench

Aging time	Alloy 6061			Alloy 2024		
	Tensile strength, MPa ^a	Yield strength, MPa ^a	Elongation, %	Tensile strength, MPa ^a	Yield strength, MPa ^a	Elongation, %
5 min	165	55	28	365	155	23
30 min	170	60	28	370	170	23
1 h	175	65	28	385	195	23
2 h	185	70	27	415	225	23
4 h	195	80	27	440	265	23
8 h	205	90	26	455	275	23
1 day	220	105	25	460	285	22
1 wk	235	125	24	465	290	22
1 mo	250	130	24	470	290	21
1 yr	260	140	23	470	290	21

^a To convert MPa to psi, multiply by 145.

Artificial Aging (Elevated Temperature Precipitation Heat Treatments). Most precipitation hardenable alloy products are usually heated at slightly elevated temperatures after solution treatment and quenching to accelerate age hardening. Effects of time and temperature on yield strength of alloy 2036 sheet are illustrated in Figure 29 (49). The T6 temper is generally used to designate material aged by the practice which produces the highest practicable strength. When cold work prior to artificial aging produces a significant positive effect on strength, the T8 temper designation is employed for material worked and aged to the highest practicable strength. Multistep aging treatments are sometimes employed to produce T7 tempers which enhance the combination of strength and resistance to exfoliation and stress-corrosion cracking of 7XXX alloy products.

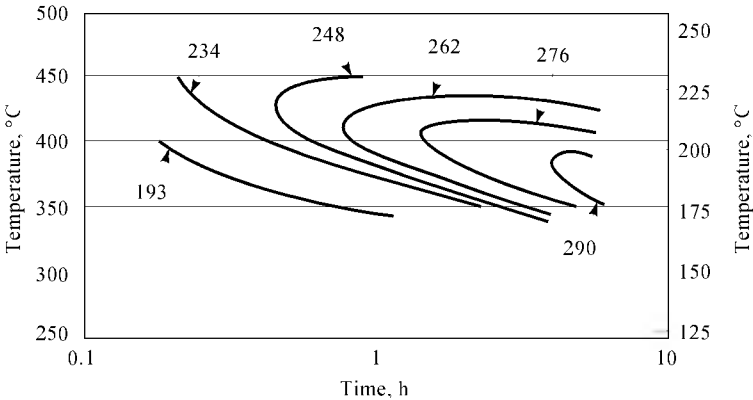


Fig. 29. Effects of time and temperature of precipitation treatments on yield strength of alloy 2036–T4 sheet. Numbers represent strength in MPa. To convert MPa to psi, multiply by 145.

Shaping and Fabricating

Aluminum alloys are commercially available in a wide variety of cast forms and in wrought mill products produced by rolling, extrusion, drawing, or forging. The mill products may be further shaped by a variety of metal working and forming processes and assembled by conventional joining procedures into more complex components and structures.

Melting and Casting. For energy savings and economy, some aluminum is alloyed and cast into ingot at smelting plants. Alloy ingot is then shipped to fabricating plants for conversion into mill products such as plate, forgings, extrusions, and tubing. Considerable scrap is generated in such mill operations, and many plants remelt the scrap and cast ingots to salvage the metal. In remelting aluminum for the production of new ingot, selected mill scrap and purchased scrap are combined with sufficient pure metal and additions in the form of alloys rich in the alloying elements. Melting temperatures are in the range of 700–750°C; casting temperatures vary with alloy but typically are about 50°C above the temperature of initial solidification.

In remelting for the production of ingot, dross is formed in substantial quantities and is collected by skimming. Dross may consist of up to 5% of the melt where clean mill scrap is used but is much higher for operations using painted foil or litter scrap. The primary components of dross are aluminum oxide and entrained aluminum plus small amounts of magnesium oxide [1309-48-4], MgO, aluminum carbide, nitride, and extraneous matter. Such dross is generally treated in rotary furnaces using fluxes of sodium chloride and potassium chloride to recover the metal values.

Scrap that is unsuitable for recycling into products by the primary aluminum producers is used in the secondary aluminum industry for castings that have modest property requirements. Oxide formation and dross buildup are encountered in the secondary aluminum industry, and fluxes are employed to assist in the collection of dross and removal of inclusions and gas. Such fluxes are usually mixtures of sodium and potassium chlorides. Fumes and residues from these fluxes and treatment of dross are problems of environmental and economic importance, and efforts are made to reclaim both flux and metal values in the dross.

Concern for the environment has prompted legislation which encourages recycling (qv) of aluminum beverage containers. Billions of used beverage containers are returned every year to the primary aluminum companies (about 60% of the aluminum cans produced in 1989 were recycled), and technology has been developed to remelt this thin scrap metal with acceptable loss from oxidation. The use of recycled metal has obviated the need for additional smelting capacity, thus saving energy and minimizing cost increases of aluminum products.

After remelting and skimming, the molten metal is treated to remove dissolved hydrogen (the only gas soluble in aluminum), inclusions, and undesirable trace elements such as sodium [7440-23-5], Na. Generally this is accomplished by bubbling chlorine or a mixture of chlorine and nitrogen through the molten metal by means of graphite tubes. In large-scale modern operations use is made of in-line filtering and fluxing systems between the holding furnace and the casting station. Choice between deep-bed filters having a counter flow of inert gas and disposable foam ceramic filters depends on quality and economic considerations (50). In-line processes are more efficient than furnace fluxing, and their use reduces hydrogen, inclusion content, and undesirable trace elements to very low levels without significant fume generation and air pollution.

Solidification of molten aluminum containing equilibrium volumes of hydrogen (Table 6) can result in significant porosity because of the greatly reduced solubility of hydrogen in solid aluminum. Commercial filtering and fluxing practices reduce hydrogen contents of the molten metal to an operating level where this is usually not a problem. Hydrogen contents of between about 0.06 and 0.2 ppm are usually obtained in the final product depending on the alloy. The solid solubility of hydrogen is considerably higher in Al–Li alloys, hence they can tolerate more hydrogen without inducing porosity (50).

Most ingot for fabrication into rolled products, forgings, or extrusions is produced by the direct chill (DC) process or a modification. The process employs a short mold having a moveable bottom. During casting the bottom of the mold is moved downward through a spray of water that cools the mold and chills the ingot. Ingot length is limited only by the supply of metal and the depth of the casting pit. The constraint of pit depth has been removed by turning the mold on its side and casting horizontally. By sawing the ingot during casting, the operation can be made continuous. Rectangular cross-section ingot for rolling flat products is typically 40 to 60 cm thick and may be as much as 120 cm in width. Ingot having a round cross section is routinely cast in diameters to 90 cm.

Since the early 1980s, electromagnetic (EM) casting, where an electromagnetic field is used to contain the molten metal during casting, has been gaining increased acceptance (51). Because the EM process provides the closest approach to continuous heat removal, the surface defects associated with the DC processes are largely eliminated. Development is continuing to solve the cracking problems associated with the complex precipitation hardenable alloys, so the process is still largely confined to strain-hardenable alloys.

Some aluminum alloys are cast as strip or rod for fabrication into sheet, foil, or wire by introducing the molten metal directly between rolls or between moving plates or steel bands that form the desired shape. Casting operations of this type have the advantage of eliminating capital investment in large break-down mills and extrusion presses. The more rapid solidification also reduces the constituent size and increases the amount of supersaturated solute. The process is limited to 1XXX, 3XXX, and certain 8XXX alloys which have a small freezing range.

Much research was done in the 1980s on other methods of solidifying aluminum alloys. One process, known as planar flow casting or melt spinning, deposits liquid aluminum onto a large rotating wheel to produce a ribbon. The advantage is that the high solidification rate allows much higher amounts of solute to be retained in supersaturated solid solution. Another process, known as Osprey or liquid dynamic compaction, produces a product or a preform by propelling molten droplets of aluminum alloy against a mandrel.

Fabrication. After the preheat or homogenization step, the ingots may be fabricated directly. Often, however, the preheated ingots are reheated in a separate operation before the first metal working operation. Bulk deformation temperatures usually range from about 350 to 450°C.

Rectangular ingots are generally broken down using a four-high reversing mill. Some gauges may be rolled to completion on a reversing mill, but thinner plate gauges are usually transferred to a series of rolling mills for fabricating to final gauge. Thicker sheet gauges, above about 5 mm, are generally hot-rolled to flat sheet on such a continuous hot line. Thinner gauges are usually coiled at an intermediate gauge as they exit the continuous hot line, annealed, then cold-rolled about 25% or more to final gauge. Sheet may be annealed and cold-rolled to foil. Thin sheet wider than the equipment used for continuous solution heat treatment must be produced by a batch process as flat sheet.

In extrusion, a heated length of ingot (billet) is forced under pressure to flow from a container through a die opening to form an elongated shape or tube. In the direct extrusion process the metal is pushed through the die. In the indirect extrusion process the die is forced into the metal. Productivity is higher using the indirect process because friction of the billet with the container walls is eliminated. The surface layers of the ingot used for the indirect process must be machined (scalped) because the surface of the billet becomes the surface of the extruded product in this process. Extrusion can economically produce many shapes, including hollows, that would be difficult or expensive to produce by alternative fabricating processes. Extruded rod or tube is frequently employed as stock in the production of drawn wire or tubing. Extrusion is sometimes used to produce starting billet for forging.

Forgings are produced by pressing or hammering ingots or billets either into simple shapes on flat dies or into complex shapes in cavity dies. Several sets of dies may be employed in arriving at the final shape. Equipment varies from simple drop hammers and mechanical presses to large hydraulic presses.

Most aluminum mill products are used in the manufacture of more complex shapes. This can be accomplished by conventional metal removal techniques and by common fabricating and joining procedures. The latter include welding, brazing, soldering, and adhesive ndashing, as well as mechanical methods of joining. Methods of fabricating include bending, deep drawing, stamping, stretch forming, impact extrusion, ironing, and swaging. The bodies of two-piece carbonated beverage cans, the largest market for aluminum sheet, are produced at high rates (about 200–300 per minute per bodymaker) by stamping a disk, drawing the disk into a cup, ironing to elongate the cup into a can, shearing to trim the can, and swaging to provide the neck.

Intricate shapes which once had to be made by joining a large number of parts are made by a process known as superplastic forming. In this process, aluminum alloy sheet that has been processed to develop an extremely fine grain size (typically about 10 micrometers in diameter) is slowly deformed either into a female die or over a male die. For those components that require metal removal, techniques include shearing, grinding, and a variety of common machining procedures. Aluminum is also being successfully processed using high speed machining techniques that employ ceramic tools and special equipment.

Corrosion

Aluminum and aluminum alloys are employed in many applications because of the ability to resist corrosion. Corrosion resistance is attributable to the tightly adherent, protective oxide film present on the surface of the products. This film is 5–10 nm thick when formed in air; if disrupted it begins to form immediately in most environments. The weathering characteristics of several common aluminum alloy sheet products used for architectural applications are shown in Figure 30. The loss in strength as a result of atmospheric weathering and corrosion is small, and the rate decreases with time. The amount of

corrosion that occurs is a function of the alloy as well as the severity of the corrosive environment. Wrought alloys of the Al, Al–Mn, Al–Mg, and Al–Mg–Si types have excellent corrosion resistance in most weathering exposures including industrial and seacoast atmospheres. Alloys based on additions of copper, or copper, magnesium, and zinc, have significantly lower resistance to corrosion.

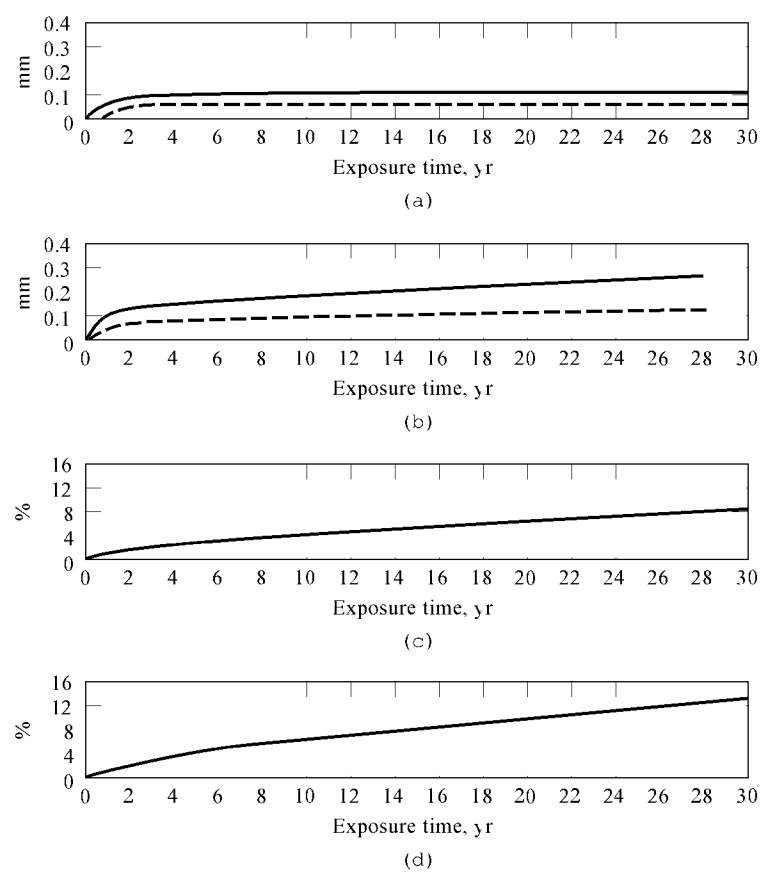


Fig. 30. Weathering of wrought aluminum alloys 1100, 3003, and 3004: (a) and (b), — maximum and — average depth of pitting-type corrosion; (c) and (d), loss in tensile strength; in industrial (a and c) and seacoast (b and d) environments.

Atmospheric corrosion is electrochemical in nature and depends on the flow of current between anodic and cathodic areas. The resulting attack is generally localized to particular features of the metallurgical structure. Features that contribute to differences in potential include the intermetallic particles and the electrode potentials of the matrix. The electrode potentials of some solid solutions and intermetallic particles are shown in Table 26. Iron and silicon impurities in commercially pure aluminum form intermetallic constituent particles that are cathodic to aluminum. Because the oxide film over these constituents may be weak, they can promote electrochemical attack of the surrounding aluminum matrix. The superior resistance to corrosion of high purity aluminum is attributed to the small number of these constituents.

Table 26. Electrode Potentials of Aluminum Solid Solutions and Intermetallic Particles

Solution	Potential, V ^a
Al ₃ Mg ₂	1.24
Al + 4 MgZn ₂	1.07
Al + 4 Zn ^b	1.05
MgZn ₂	1.05
Al ₂ CuMg	1.00
Al + 1 Zn ^b	0.96
Al + 7 Mg ^b	0.89
Al + 5 Mg ^b	0.87
Al Mn	0.85
99.95 Al	0.85
Al + 1 Mg ₂ Si	0.83
Al + 1 Si ^b	0.81
Al + 2 Cu ^b	0.75
Al ₂ Cu	0.73
Al + 4 Cu ^b	0.69
Al ₃ Fe	0.56
Al ₃ Ni	0.52
Si	0.26

^a 0.1 N calomel scale, measured in an aqueous solution of 53 g L NaCl + 3 g L H₂O₂ at 25°C.

^b Solid solution.

Intermetallic particles formed by interaction of aluminum and alloying elements such as copper, magnesium, lithium, and zinc also have electrode potentials that differ from those of aluminum or the solid solutions in which they exist. If such particles are finely divided and uniformly distributed, their effect on corrosion is minimal. During quenching or aging treatments, however, precipitates may localize at grain boundaries, and render them susceptible to intergranular exfoliation corrosion or stress-corrosion cracking (SCC). In the 1960s, a series of tempers was developed for commercial Al–Cu–Mg–Zn alloys which modify the precipitate structure so that the products are highly resistant to these phenomena (52) even in the short-transverse direction. These tempers are designated T73, highly resistant to both SCC and exfoliation corrosion; T76, resistant to exfoliation corrosion and more resistant to SCC than

products in T6 tempers, and T74, corrosion characteristics intermediate to T73 and T76. Because the strength of products in these T7 tempers was as much as 20% less than that possible using the T6 temper, in the late 1980s a process was developed that provided T6 strength and T76 corrosion characteristics (50). The process was first commercialized on alloy 7150 in the T77 temper. This material has been specified for upper wing skins and other aircraft structure that is dominated by compressive loading.

The resistance to corrosion of some alloy sheet is improved by cladding the sheet with a thin layer of aluminum or aluminum alloy that is anodic to the base alloy. These anodic layers are typically 5–10% of the sheet thickness. Under corrosive conditions, the cladding provides electrochemical protection to the core at cut edges, abrasions, and fastener holes by corroding preferentially. Aircraft skin sheet is an example of such a clad product.

Aluminum alloys are used widely for processing, handling, and storing a variety of chemicals. Aluminum generally has a high resistance to corrosion by chemical solutions in the pH range of 4.5–8.5 because the protective oxide film is relatively stable within this range. In strongly acidic or alkaline solutions, the film is less stable and resistance to corrosion is impaired. Dry inorganic salts are usually not corrosive to aluminum. Organic acids and alcohols can be handled in aluminum equipment if a trace of water is present to maintain the oxide film.

Finishes for Aluminum

Finishes for aluminum products can be both decorative and useful. Processes in use include anodic oxidation, chemical conversion coating, electrochemical graining, electroplating (qv), thin film deposition, porcelain enameling, and painting. Some alloys respond better than others to such treatments.

Anodic oxidation is an electrochemical process in which the oxide film is increased in thickness by making the product the anode in a cell containing a suitable electrolyte and an inert cathode (see ELECTROCHEMICAL PROCESSING). Sulfuric acid solutions are widely employed as electrolytes for anodizing; they produce clear oxide coatings on pure aluminum and high purity Al–Mg and Al–Mg–Si alloys. As the purity of the metal decreases, iron and silicon and other impurities and their reaction products form in the oxide film and decrease its transparency. This imparts a gray appearance to the finish. Sheet for reflectors and for automotive and appliance trim is made from high purity alloys to obtain maximum brightness and specularity. Oxide thickness generally does not exceed 0.01 mm for such products. Colored oxide films are produced by anodizing in mixed acid electrolytes the principal components of which are organic sulfonic acids and a small amount of sulfuric acid. Colors range from pale yellow to dark bronze and black. The color results from modification of the oxide and inclusion of intermetallic particles, metal, and reaction products in the oxide. Such coatings are widely employed in architectural applications for aluminum and are usually 0.02–0.03 mm thick.

Thin, porous anodic films provide an excellent base for paint (qv) coatings (qv), as do certain chemical and mechanical treatments. These are employed to disrupt the natural oxide film on aluminum and eliminate contaminants that would interfere with wetting of the surface by organic coatings. Chemical conversion coatings convert a portion of the base alloy to one of the components of a chemical film which is then integral with the metal surface. Carbonate, chromate, and phosphate films are produced in this manner and have excellent adhesion qualities. Chemically produced metallic coatings (qv) are also used extensively to provide a base for organic coatings. The zinc immersion coating is the most widely employed of the chemical displacement films.

Zinc, tin, and nickel immersion coatings are used as a base for electroplating. Anodizing and mechanical roughening treatments are also employed. Good surface preparation is required for good adherence of electrodeposits, which can be of any commonly electroplated metal. Electroplating conditions and solutions are the same as those for steel and other metals (see METAL SURFACE TREATMENTS). Deposition of thin films of oxides or other ceramics by vapor deposition or other means is beginning to be commercially applied to aluminum products (see FILM DEPOSITION TECHNIQUES).

Porcelain enameling requires the use of frits and melting temperatures of 550°C or below. Enamels are applied over chemical conversion coatings that are compatible with the frit. Alloy selection is important to obtain good spall resistance. Alloys 1100, 3003, and 6061 are employed most extensively among wrought products and alloy 356 for castings.

Uses

Packaging has replaced the building and construction industry as the largest consumer of aluminum in the United States because aluminum is impermeable to gas, resistant to corrosion, and recyclable. The most prominent has been the use of aluminum for beer and carbonated beverages. Over 95% of the beer and carbonated soft drinks are packaged in two-piece aluminum cans. Alloys 3004 and 5182 are used for can bodies and ends, respectively. Aluminum has long dominated the market for short, convenience-type cans with easy-open lids, which contain foods such as meat, pudding, and fish; and it is beginning to make headway into the market for larger food cans (eg, pet food cans). Aluminum is also used in aerosol cans (see AEROSOLS), and as foil–plastic–paper laminates for packaging a variety of cereal, frozen food, and nonfood products. Formed light-gauge sheet and foil are also used for frozen food trays, pie plates, and similar products (see FOOD PACKAGING).

The largest market worldwide for aluminum products is in the building and construction industry. Alloys such as 3003, 3004, and 3105 are employed for residential siding, industrial roofing and siding, and farm roofing and siding. Gutters and downspouts are also fabricated from these alloys. Doors and windows are usually produced from 6063 extrusions. Screening, nails, and other fasteners are made from high strength Al–Mg or Al–Mg–Si alloys. Aluminum sheet is used in sandwich structures with insulation and foamed plastics for interior applications in industrial construction. Anodized and colored aluminum panels are also used in the curtain wall structures of many buildings and for store fronts and other decorative applications. Good resistance to weathering, adequate strength, and light weight for ease of handling are the characteristics of aluminum in these applications (see BUILDING MATERIALS, SURVEY).

Because of aluminum's low density, the field of transportation is another large market for aluminum alloys. In commercial and military aircraft, heat-treatable Al–Cu–Mg and Al–Cu–Mg–Zn alloys such as the 2X24, 7X75, and 7X50 series are used for both supporting structure and skins for wings, fuselages, and other components. The alloy, temper, and product of choice for each application depends on mechanical properties such as strength, fracture toughness, behavior under cyclic loads (fatigue), and corrosion and stress-corrosion characteristics. Because of their low density, Al–Cu–Li and Al–Cu–Li–Mg alloys have been specified for some aircraft of the 1990s despite their higher cost. A high strength Al–Cu–Mg–Si alloy, 6013, has found use because of its formability and corrosion characteristics. Weldable Al–Cu alloys are used extensively for satellites and space vehicles.

ARALL laminates, a family of hybrid composites consisting of aramid fibers bonded with epoxy between 0.3 mm thick aircraft alloy sheets, were introduced in the 1980s (53). The laminates have lower density than even the new Al–Li alloys and are greatly superior to monolithic aluminum sheet in resisting the growth of fatigue cracks. ARALL laminates have been specified for aircraft structure which is subjected to cyclic tension loads (see LAMINATES).

Aluminum is also used in other transportation industries. In automobiles, aluminum alloys are used for engine blocks, hood and trunk lids, wheels, interior and exterior trim, grilles, bumpers, radiators, oil coolers, air conditioners, intake manifolds, water pumps, and automatic transmissions. A variety of alloys are used depending on the properties and finishing requirements. Driving forces for the use of aluminum alloys are the light weight for fuel economy and low cost compared to competing materials for trim, bumpers, and heat exchangers. Several auto companies are exploring the possibility of manufacturing aluminum-intensive vehicles where aluminum alloy sheet or castings replace steel for load-bearing structure. In commercial automotive applications, aluminum is used in truck cabs and bodies, for wheels and some engine components to reduce weight and increase payload. Aluminum is also used in rapid transit, recreational vehicles, rail freight and tank cars, engine parts for diesel locomotives, and in buses for bodies, bumpers, and engine parts. Highway signs, divider rails, highway lighting standards, and bridge decks are made from a number of aluminum alloys. In marine service, Al–Mg and Al–Mg–Si alloys are used for canoes, pleasure boat and Hovercraft hulls, fishing boats, tanks for liquefied natural gas, and deck houses for naval vessels.

Aluminum is used in the home as household foil (0.18 mm thick), cooking utensils (the first commercial use of aluminum), refrigerators, air conditioners, appliances, insect screening, and hardware. It is also used for toys, sporting equipment, lawn furniture, lawn mowers, and portable tools. In many of these applications, anodized or colored coatings are employed for decorative purposes.

Aluminum is an excellent conductor of electricity, having a volume conductivity 62% of that of copper. Because of the difference in densities of the two metals, an aluminum conductor weighs only half as much as a copper conductor of equal current carrying capacity. Because of its lightness, aluminum

has been used extensively for overhead transmission lines . Both stranded aluminum conductors and steel core stranded conductors are employed. Alloys include conductor grades 1350 and 6201 along with newer compositions. Aluminum is also used as cable sheathing, replacing the neutral in three-phase systems. Aluminum is used in insulated cable, for bus bars, and for transformer windings, magnet wire, building wire, and 99.99^o aluminum is used to connect integrated circuits.

Aluminum has many applications in the chemical and petrochemical industries such as for piping and tanks in alloys 1100, 3003, 6061, 6063, and the Al–Mg alloys. Aluminum is chosen for its resistance to corrosion by the chemicals involved as well as for its mechanical properties, light weight, and thermal conductivity. Aluminum is also used in the storage and packaging of chemicals. Applications range from large Al–Mg alloy tanks for the storage of ammonium nitrate and liquefied natural gas to collapsible tubes for dispensing pharmaceuticals and toiletries. The absence of any harmful reaction with the microorganisms involved in the manufacture of pharmaceuticals is obviously important in this application of aluminum.

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ALUMINUM COMPOUNDS

Introduction,
Aluminates,
Aluminum carboxylates,
Aluminum halides and aluminumnitrate ,
Aluminum oxide(Alumina),
Aluminum sulfate and alums,
Polyaluminums,

INTRODUCTION

Aluminum [7429-90-5], Al, atomic number 13, atomic weight 26.981, is, at 8.8 wt % , the third most abundant element in the earth's crust. It is usually found in silicate minerals such as feldspar [68476-25-5], clays, and mica [12001-26-2]. Aluminum also occurs in hydroxide, oxide–hydroxide, fluoride, sulfate, or phosphate compounds in a large variety of minerals and ores.

The CAS registry lists 5,037 aluminum-containing compounds exclusive of alloys and intermetallics. Some of these are listed in Table 1. Except for nepheline and alunite in the USSR and Poland, bauxite is the raw material for all manufactured aluminum compounds. The term bauxite is used for ores that contain economically recoverable quantities of the aluminum hydroxide mineral gibbsite or the oxide–hydroxide forms boehmite and diaspore.

Table 1. Aluminum Compounds Referred to in Text

Compounds	CAS Registry Number	Molecular formula
alum	[7784-24-9]	KAl(SO ₄) ₂ ·12H ₂ O
alumina	[1344-28-1]	Al ₂ O ₃
aluminum bromide	[77727-15-3]	AlBr ₃
aluminum chlorhydroxide (ACH)	[12042-91-0]	Al ₂ Cl(OH) ₅
aluminum(I) chloride	[13595-81-8]	AlCl
aluminum(III) chloride	[7446-70-6]	AlCl ₃
aluminumchloride hexahydrate	[7784-13-6]	AlCl ₃ ·6H ₂ O
aluminum(I) fluoride	[13595-82-9]	AlF
aluminum(III) fluoride	[7784-18-1]	AlF ₃
aluminum hydroxide	[21645-51-2]	Al(OH) ₃
aluminum iodide	[7784-23-8]	AlI ₃
aluminum(II) oxide	[14457-64-8]	AlO
aluminum silicate	[12141-46-7]	Al ₂ (SiO ₃) ₃
aluminum sulfate	[10043-01-3]	Al ₂ (SO ₄) ₃
aluminum sulfate octadecahydrate	[7784-31-8]	Al ₂ (SO ₄) ₃ ·18H ₂ O
alunite	[12588-67-9]	K ₂ Al (SO ₄) ₄ (OH) ₁₂
anorthite	[1302-54-1]	CaO ·Al ₂ O ₃ ·2SiO ₂
bauxite	[1318-16-7]	
boehmite	[1318-23-6]	AlO(OH)
calcium aluminate	[12042-78-3]	Al ₂ O ₃ ·3CaO
corundum	[1302-74-5]	α-Al ₂ O ₃
diaspore	[14457-84-2]	α-AlO(OH)
gibbsite	[14762-49-3]	α-Al(OH) ₃
halloysite	[12244-16-5]	Al ₂ Si ₂ O ₅ (OH) ₄ ·2H ₂ O
kaolin	[1332-58-7]	H ₂ Al ₂ Si ₂ O ₈ ·H ₂ O
kaolinite	[1318-74-7]	Al ₂ O ₃ ·2SiO ₂ ·2H ₂ O
kyanite	[1302-76-7]	H O ₅ Si ·2Al
montmorillonite	[1318-93-0]	
nepheline	[12251-27-3]	NaAl(OH)SiO ₃
nepheline	[12251-28-4]	NaAl ₂ (OH) ₂ (SiO ₃) ₂ ·H ₂ O
nepheline	[14797-52-5]	AlH ₄ O ₄ Si
sapphire	[1317-82-4]	Al ₂ O ₃
sodium aluminate	[1302-42-7]	NaAlO ₂
triethylaluminum	[97-93-8]	(C ₂ H ₅) ₃ Al
triisobutylaluminum	[100-99-2]	(C ₄ H ₉) ₃ Al
zeolite A	[1318-02-1]	Na ₁₂ [(Al ₁₂ Si ₁₂)O ₄₈] ·27H ₂ O
zeolite Y		Na ₅ [(AlO ₂) ₅ (SiO ₂) ₁₃] ·250H ₂ O
zeolite X		Na ₈ [(AlO ₂) ₈ (SiO ₂) ₁₀] ·264H ₂ O

Western-world bauxite production in 1988 totaled about 90 × 10⁶ t, approximately 90% of which was refined to aluminum hydroxide by the Bayer process. Most of the hydroxide was then calcined to alumina and consumed in making aluminum metal. The balance, which constituted about 2.3 × 10⁶ t in 1988 (Table 2), was consumed in production of: abrasives (qv); adhesives (qv); calcium aluminate cement used in binding ceramics (qv) and refractories (qv); catalysts used in petrochemical processes and automobile catalytic converter systems (see PETROLEUM; EXHAUST CONTROL, AUTOMOTIVE); ceramics that insulate electronic components such as semiconductors and spark plugs; chemicals such as alum, aluminum halides, and zeolite; countertop materials for kitchens and baths; cultured marble; fire-retardant filler for acrylic and plastic materials used in automobile seats, carpet backing, and insulation wrap for wire and cable (see FLAME RETARDANTS); paper (qv); cosmetics (qv); toothpaste manufacture; refractory linings for furnaces and kilns; and separation systems that remove impurities from liquids and gases.

Table 2. World Production of Bauxite and Bauxite Products, 10⁶ t/yr

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Product	1980	1985	1988
bauxite refined to alumina	80	77.6	81
bauxite for other uses	9.0	7.4	9.0
<i>Total bauxite produced</i>	<i>89</i>	<i>85</i>	<i>90</i>
alumina consumed for metal production ^a	29.9	29.7	31
alumina to aluminum chemicals	2.9	2.2	2.3
<i>Total alumina produced</i>	<i>32.8</i>	<i>31.9</i>	<i>33.3</i>
<i>Total primary metal production</i>	<i>15.4</i>	<i>15.3</i>	<i>16</i>

^a An ore factor of 1.94 Al₂O₃/Al accounts for impurities in the ore that do not report to the metal pad, ie, Na₂O, H₂O, and CaO.

Aluminum compounds, particularly the hydroxides and oxides are very versatile. Properties range from a hardness indicative of sapphire and corundum to a softness similar to that of talc [14807-96-6] and from inertness to marked reactivity. Aluminas that flow and filter like sand may be used for chromatography (qv); others are viscous, thick, unfilterable, and even thixotropic (1).

Bauxite Production

The term bauxite originates from the location of the deposit discovered in 1821 near the village of Les Baux in Provence, France. Bauxite is weathered rock consisting mainly of aluminum hydroxide minerals but having small and variable amounts of silica [7631-86-9], the iron oxides hematite [1309-37-1], Fe₂O₃, and magnetite [1317-61-9], Fe₃O₄, rutile or titanium oxide [1317-80-2], and alumina silicate clays. Deposits were formed over many geologic time periods in a tropical or subtropical climate having enough rainfall and circulating groundwater to dissolve constituents of the parent rock and carry them away. Weathering is intensified by good drainage and by decaying vegetation, which makes the process acidic. Table 3 gives typical compositions for bauxites found throughout the world.

Table 3. Composition of Bauxite Used for Alumina Production

Location	Constituents, wt %				Loss on ignition (LOI), %	Mineral components
	Al ₂ O ₃	SiO ₂	Fe ₂ O ₃	TiO ₂		
Australia						
Weipa	54.8	5.3	5.20			gibbsite, some boehmite
Gove	50	3.4–4.2	17.1	3.4	26.4	gibbsite, some boehmite
Darling Range	30–35	0.3–2.0	10–25			gibbsite, trace boehmite
Brazil						
Trombetas	55.9	4.8	9.4	1.3	28.6	gibbsite, <1% boehmite
France	53.0	7.8	21.4	2.6	13.3	boehmite
Greece	57.6	3.0	22.8	2.75	12.17	boehmite, some diaspor
Guinea						
Boke-Sangaredi	59.1–59.6	0.7–0.9	4.9–5.9	3.3–3.5	30.6–31.0	83–86% gibbsite, 3.5–5.5% boehmite
Fria	45.5	4.0	23.6	2.5	23.9	gibbsite
Guyana	55–61	1–10	0.8–5	2–5	30–35	nearly pure gibbsite
Hungary	50–60	1–5				boehmite, some gibbsite
India						
Ranchi	51–60	0.1–5	4–10	0.3–17	22–28	gibbsite, some boehmite
East Coast province	43.7–56.5	0.5–4.2	8.6–38.4	2.1–3.5	24.6–30.5	gibbsite, <5% boehmite
Jamaica	49.1–50.6	0.7–6.1	18.9–20	2.5–2.7	24.6–27.3	gibbsite, 7–10% boehmite
Surinam	58.5–60	3.4–4.3	2.7–4.4	2.4–2.7	30.7–31.4	nearly pure gibbsite
United States	45–50	13	8	2.5–3	25 ±	gibbsite, SiO ₂ is mainly in kaolinite
USSR	45–55	2–10	5–15			boehmite; some mixed with diaspor
Yugoslavia	56–58	3–5	20–22	2.5–2.7	13.0	boehmite, SiO ₂ in kaolinite

Uses of bauxite other than for aluminum production are in refractories, abrasives, chemicals, and aluminous cements. Bauxites for these markets must meet more rigid compositional requirements with respect to Fe₂O₃, SiO₂, and TiO₂ content than those used for alumina production.

The largest world bauxite resources are in Africa, Australia, South America, and the Caribbean, although significant deposits are also present in Asia and Europe. As can be seen from Table 4, Guinea has the world's largest bauxite reserve, estimated to be 5.6 billion metric tons (2–5).

Table 4. World Bauxite Production and Reserves, 10³ t

Country	Annual production		Reserves
	1988	1989 ^a	
United States	588	615	38,000
Australia	36,192	37,000	4,440,000
Brazil	8,750	8,800	2,800,000
Greece	2,400	2,550	600,000
Guinea	15,600	16,800	5,600,000
Guyana	1,774	1,000	700,000
India	3,829	3,900	1,000,000
Jamaica	7,408	8,300	2,000,000
Surinam	3,434	3,400	575,000
Venezuela	700	800	320,000
Yugoslavia	3,034	3,100	350,000
other market economy countries	3,844	3,700	2,600,000

Hungary	2,906	2,600	300,000
USSR	4,600	4,600	300,000
other centrally planned economies	3,800	3,800	200,000
World total (may be rounded)	98,859	101,000	21,800,000

^a Estimated.

Bauxite exists in many varieties. The physical appearance ranges from earthy dark brown ferruginous material to cream or light pink-colored layers of hard, crystalline, gibbsitic bauxite. Ores composed chiefly of gibbsite, $\alpha\text{-Al(OH)}_3$, are commonly termed trihydrate bauxites or the Surinam type; those composed of boehmite, AlO(OH) , are called monohydrate bauxite, or the European type; and those composed of a mixture of gibbsite and boehmite are referred to as mixed bauxites. The term Jamaica type is applied to very fine-grained gibbsitic bauxite ore containing $<10\%$ boehmite. Diaspore, $\alpha\text{-AlO(OH)}$, is the major constituent of bauxites in Greece, Romania, Russia, and China.

Iron and titanium minerals commonly found in bauxites are hematite, goethite [1310-14-1], FeO(OH) , siderite [14476-16-5], FeCO_3 , magnetite, ilmenite [12168-52-4], FeTiO_3 , anatase [1317-70-0], TiO_2 , and rutile. Silicon dioxide may occur as quartz [14808-60-7], but it is silica associated with the clay (qv) minerals kaolite, halloysite, or montmorillonite that is important in processing bauxite for alumina production. These aluminosilicates react during the extraction stage of alumina production to form insoluble sodium aluminum silicates resulting in losses of NaOH and Al_2O_3 . The amount of this reactive silica is one of the bauxite quality and price-determining factors (6). Some ores, Brazilian Trombetas, for example, are upgraded by washing some of the fine kaolin away.

Hardness, texture, and the amount of overburden determine the methods for mining bauxite. Tropical gibbsitic bauxites are usually located so close to the earth's surface that strip mining can be used. However, European bauxites frequently require mining to depths of several hundred meters. The Bayer process, patented in 1888 (7), involved hot leaching of bauxite with NaOH solution in pressure vessels to obtain a supersaturated sodium aluminate solution from which Al(OH)_3 was precipitated by seeding. This process achieved immediate industrial success, replacing the soda ash roasting of bauxite used to form leachable sodium aluminate. Development of the Bayer process also coincided with the rapid increase in demand for pure alumina to be used in metal production by the Hall-H roult process discovered in 1886 (see ALUMINUM AND ALUMINUM ALLOYS).

Figure 1 illustrates the Bayer process as it is practiced in the 1990s. The primary purpose of a Bayer plant is to process bauxite to provide pure alumina for the production of aluminum. World production of Al(OH)_3 totaled ca 55×10^6 t in 1988. Practically all of the hydroxide was obtained by Bayer processing and 90% of it was calcined to metallurgical grade alumina (Al_2O_3). However, about 10% of the bauxite processed serves as feedstock to the growing aluminum chemicals industry.

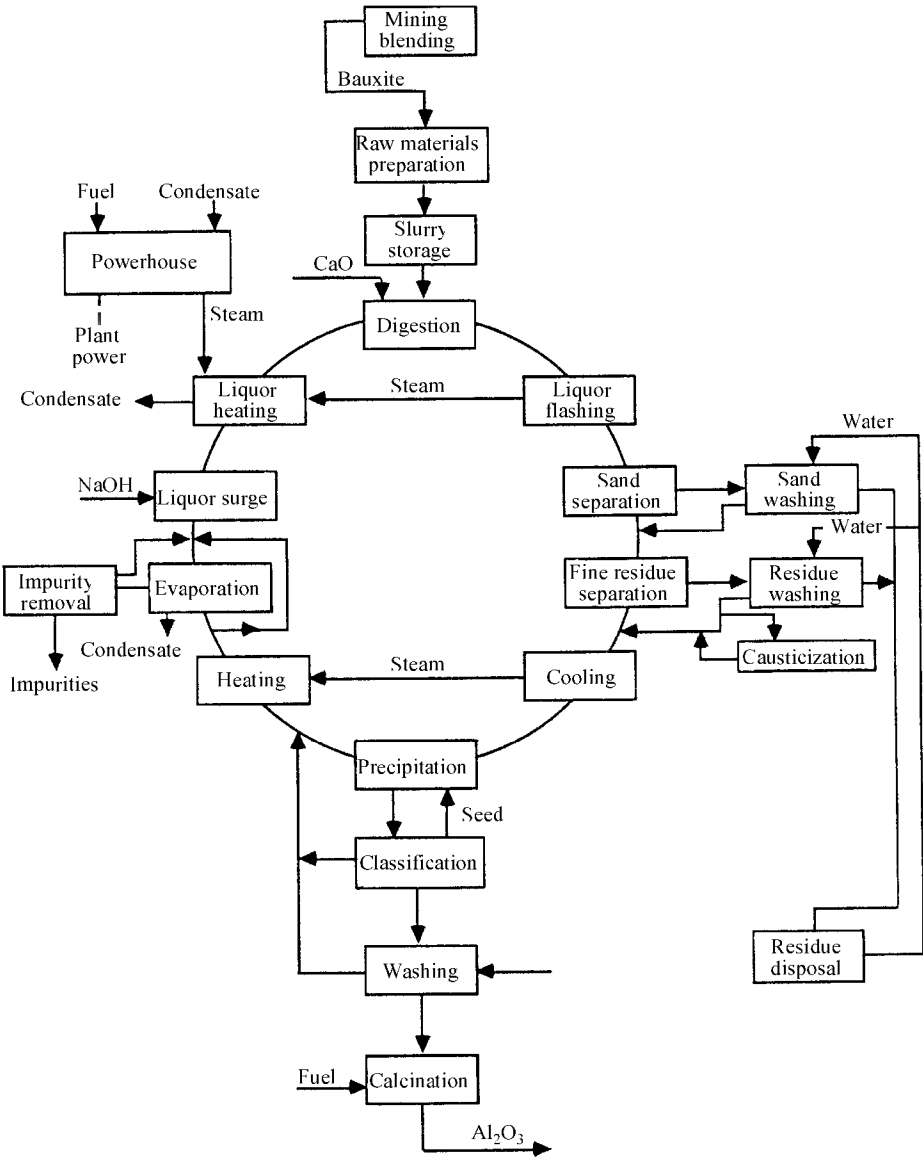


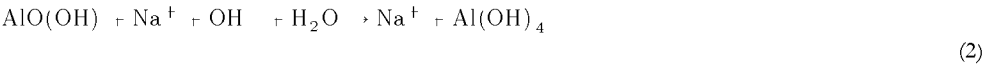
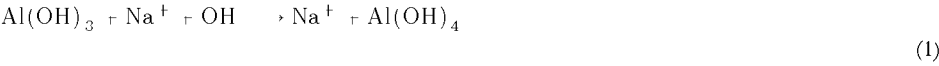
Fig. 1. Bayer process flow sheet.

Bauxite grade, mineralogy, composition, uniformity and location of the ore deposit, site infrastructure, availability of low cost energy, and designer bias, as well as legislative and environmental restrictions all affect Bayer plant design. All bauxite refineries share six common process steps: bauxite mining; raw material preparation; bauxite digestion; separation, washing, and disposal of insoluble bauxite residue; aluminum hydroxide (trihydrate) precipitation; and calcination to anhydrous alumina.

Additional operations essential to commercial bauxite processing are steam and power generation, heat recovery to minimize energy consumption, process liquor evaporation to maintain a water balance, impurity removal from process liquor streams, classification and washing of trihydrate, lime caustication of sodium carbonate [497-19-8] to sodium hydroxide [1310-73-2], repair and maintenance of equipment, rehabilitation of mine and residue disposal sites, and quality and process control. Each operation in the process can be carried out in a variety of ways depending upon bauxite properties and optimum economic tradeoffs.

Mining and Ore Preparation. Bauxite mining practice is dictated by the nature of the ore body. Blending operations, physical beneficiation (washing out clay slurries), and bauxite drying are used if the ore body is not uniform, contains an excessive amount of kaolin (clay) that would consume caustic, or is difficult to handle because of its moisture content (see CLAYS). Grinding is designed to produce feed material small enough to ensure easy alumina extraction yet coarse enough to avoid clarification problems with bauxite residue. Uniform, consistent, easily digested bauxite slurry is formed by blending properly ground bauxite slurry in slurry storage "surge" tanks prior to digestion.

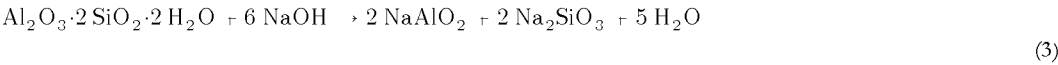
Digestion. Digestion extracts and solubilizes the available aluminum minerals from the bauxite. Digest conditions and equipment vary widely, depending on bauxite mineralogy, ie, the solution rates of the ore, and on achieving high productivity from a given liquor flow rate. In digestion, which is performed in steel vessels, autoclaves, or tubular reactors, hot spent liquor reacts with the aluminum minerals in the bauxite to form soluble sodium aluminate. Virtually all the other constituents are rejected as undissolved solids.



The term spent liquor is used to distinguish recycled sodium hydroxide solution containing a low amount of dissolved sodium aluminate from the "green" or "pregnant" liquor leaving digestion that has a high sodium aluminate content. Liquor concentrations are expressed as g/L of a given constituent and depending upon the refinery location, the total caustic content, including that tied up as sodium aluminate, is expressed as g/L NaOH, Na₂CO₃, or sodium oxide [1313-59-3], Na₂O.

Gibbsitic bauxite, Equation 1, is the most economical to process because of gibbsite's high solubility in Bayer process liquor at moderate temperature and pressure. Liquor containing 120–135 g/L Na₂O is used at about 140°C. Although boehmite and diaspor have the same chemical composition (AlOOH), diaspor is denser and harder than boehmite. Boehmitic bauxite requires temperatures from 200–250°C and pressures of 3.45 MPa (34 atm) or higher to obtain complete extraction and form high ratio green liquors. This ratio, which ultimately determines liquor productivity, is the g/L Al₂O₃ dissolved divided by the g/L Na₂O in solution. Processing diasporic bauxite requires stronger caustic solutions, 200–300 g/L Na₂O, in addition to higher temperatures and pressures. Whereas some bauxites may be composed entirely of one aluminous mineral phase, others may contain all three aluminum hydroxide minerals and the mineral most difficult to extract sets the digest conditions.

Other important reactions that occur in digestion are desilication, causticization of liquor, and precipitation of impurities. The reactive silica in bauxite, for example that in kaolin, reacts with caustic to form soluble sodium silicate [1344-09-8], Na₂SiO₃



which then reacts at digest temperature to form an insoluble sodium aluminum silicate known as desilication product (DSP), the most probable formula of which is 3 Na₂O · 3 Al₂O₃ · 6 SiO₂ · 2 Na₂X · YH₂O, where X can be any of a number of anions, including CO²⁻₃, SO²⁻₄, Cl⁻, OH⁻, and Al(OH)₄⁻, all of which are present in Bayer liquors. Good desilication is effected by high temperatures and holding times and is essential for product purity.

Causticization, the reaction of hydrated lime [1305-62-0], Ca(OH)₂, with sodium carbonate to regenerate sodium hydroxide and precipitate calcium carbonate, is an important part of the Bayer process chemistry.



Na₂CO₃ is formed in Bayer liquors by caustic degradation of the organics (humic acids) in bauxite and by absorption of CO₂ during exposure of process liquors to the atmosphere. Although poor lime efficiency and alumina losses during digestion as calcium aluminates have led to the practice of "outside" causticization of dilute green liquor flows in the residue washing area of the plant, digestion lime additions are still made to control impurities such as phosphorous pentoxide [1314-56-3], P₂O₅.

Clarification. Clarification is the term used to describe separation of bauxite residue solids from the supersaturated green liquor near its boiling point. Coarse particles, called sand because of the high silica content, are usually removed by cycloning followed by washing on sand classifiers prior to disposal. In most plants, the fine fraction of residue is settled in raking thickeners with the addition of flocculants to improve the clarity of thickener overflow. The concentrated thickener underflow is washed before disposal in countercurrent decantation washers (similar to the raking thickeners) or on vacuum drum-type filters, or a combination of both. Thickener overflow is filtered to remove the final traces of solids and ensure product purity. Kelly-type pressure filters are most widely used, but some plants use sand filters in which the liquor is filtered by gravity through a bed of properly sized sand. Filtered solids are removed from filter press cloth by hosing and are elutriated from the sand by backwashing.

Precipitation. Precipitation is the heart of the Bayer plant where recovery of the Al(OH)₃ from process liquors occurs in high yield and product quality is controlled. The dominant use for Bayer Al(OH)₃ is to calcine it into smelting grade alumina.

Cooling after digestion and clarification enhances the supersaturation of dissolved Al(OH)₃, but the solution remains metastable and autoprecipitation, which would result in losses during clarification, still is not rapid. The liquor is usually seeded with fine gibbsite seed from previous cycles to initiate precipitation. This reaction is the reverse of Equation 1, except that seed is present so that agglomeration and creation of new particles occur simultaneously. Maintaining a seed balance around precipitation and classification is important in achieving good yield and proper particle size, ie, the number of particles created in precipitation should equal the number leaving the system as product. Thus, nucleation, agglomeration, particle growth, and particle breakage need to be balanced. Problems arise because of the lack of a complete understanding of the interaction among variables such as specific precipitation rate (SPR), residence time, liquor concentrations, inorganic and organic impurities, mixed and split seeding, active vs poisoned seed area, seed retention, temperature profiles, and the effect on yield and product quality.

Precipitation can be continuous or batch. Modern plants use the continuous system where 10 to 14 flat-bottom, internally agitated tanks, approximately 30 m in height and 10–12 m in diameter, are placed in series so that flow of the liquor–seed slurry moves by gravity through launders connecting the tank tops.

Classification. Slurry leaving precipitation is classified into a coarse and one or more fine fractions, usually by elutriation in hydroclassifiers. Cyclones and combinations of hydroclassifiers and cyclones are gaining popularity. In smelting grade alumina plants, the coarse fraction, called primary product, is sent to calcination; the fine fractions, called secondary and tertiary seed, are recycled to be grown to product size.

Calcination. Calcination, the final operation in production of metallurgical grade alumina, is done either in rotary kilns or fluid bed stationary calciners at about 1100°C. Prior to calcination, the process liquor is washed from the Al(OH)₃ using storage tanks and horizontal vacuum filters. During heating, the trihydroxide undergoes a series of changes in composition and crystal structure but essentially no change in particle shape. The product is a white powder consisting of aggregates ranging in size from 20 μm to about 200 μm. Details of the calcination process are given in the literature (8–10).

Evaporation and Impurity Removal. Evaporation over and above that obtained in the cooling areas from flashed steam is usually required

to maintain a water balance by removing dilution arising from residue and $\text{Al}(\text{OH})_3$ washing, free moisture in the ore, injected steam, purge water, and uncontrolled dilutions. Evaporation also serves to concentrate impurities in the liquor stream such as sodium oxalate [62-76-0], $\text{Na}_2\text{C}_2\text{O}_4$, a product of organics degradation, making impurity removal easier.

Energy Conservation. Cogeneration of steam and power is usually an integral part of a Bayer plant, unless there is abundant low cost (usually hydroelectric) power available from an existing grid. The cogeneration feature enables fuel efficiencies of ~85% compared to ca 35% in public utilities power plants where turbine exhaust steam is merely condensed and recycled rather than being used for process heating.

Minimizing energy consumption per ton of alumina while maintaining a steam-power balance is an industry-wide, ongoing effort. Reduction of steam consumption has been limited by the cost of purchased power to compensate for loss of power generation.

In most plants heat recovery from the hot slurry leaving digestion is accomplished by flashing the slurry through a series of pressure vessels (flash tanks) to its atmospheric boiling point. The steam evolved accounts for a significant amount of the evaporation needed to maintain a water balance. It is used to heat the liquor returning to digestion before being recycled to the powerhouse boilers. Heat recovery from clarified liquor to precipitation is done in an analogous system, but because the liquor is cooled below its boiling point, flash vessels and heat exchangers must operate under vacuum.

Residue Disposal. The major environmental problem in the Bayer process is disposal of bauxite residue which is effected by marine disposal, lagooning, use of underdrain lakes, or semidry disposal. Marine disposal in oceans or rivers, diluting the alkaline residue by large quantities of water, is environmentally unacceptable. Lagooning behind retaining dikes built around clay-sealed ground is commonly used, but there have been isolated leaks into aquifers. This has motivated installation of underdrains between the residue and clay-sealed, plastic-lined, lake bottom. This design removes the hydraulic head from the lake bottom and improves consolidation of the residue.

The newest method is semidry disposal, sometimes referred to as dry-stacking, or the drying field method of disposal, which takes advantage of the thixotropic nature of the residue. In this method, the residue is concentrated by vacuum filtration or other means to 35–50% solids. The percent solids required depends on residue rheology which varies as the source of the bauxite. Using agitation and or additives, the viscosity of the concentrated slurry is reduced so it can be pumped to the disposal area where it flows like lava, establishing a gentle slope away from the discharge point. The slurry is called nonsegregating because neither water nor sand separate from it. In the absence of shear, the viscosity increases and flow stops. Any rainwater rapidly drains to the perimeter of the deposit. There is no free water on the surface of the impoundment, so the deposited residue dries and cracks whenever it is not raining. When the percent solids approaches 70–75%, bulldozers can work on the deposit. This method of disposal provides maximum storage for a given area and easy recovery if, in the future, any economical use for the residue is found. The disadvantages include a need for dust control and a separate cooling pond for the plant.

To return land once devoted to bauxite residue disposal to productive use, abandoned semidry disposal areas can be contoured and landscaped into surroundings capable of supporting homes and or light industrial buildings. In the case of lagoons and lakes, the land has been returned to agricultural use. This has been accomplished, particularly in Australia, by dewatering (qv) abandoned lakes, covering them with several meters of neutral sand, and adding fertilizer to support crop growth.

Alternative Processes. Bayer processing of bauxite is the most economical method for $\text{Al}(\text{OH})_3$ and Al_2O_3 production; however, the lime–soda sintering process (6,11) is available to treat the high silica bauxites in the United States and nepheline in the USSR. In the lime-soda process, leachable sodium aluminate is formed and silica is insolubilized by reaction with calcium. Research has shown that alumina production from nonbauxitic raw materials such as clay, anorthosite, alunite, coal waste, and oil shale (qv) has been technically feasible (12–14), but these technologies cannot compete with the Bayer process economically. The one that comes closest is acid (HCl) processing of clay (see CLAYS).

Bauxite Economics

There are about 40 Bayer refineries located throughout the world. Alumina, Al_2O_3 , production capacity, which ranges from 100,000 to 3,000,000 t yr, is summarized in Table 5. The smaller plants produce products solely for chemical applications; the larger refineries are almost fully devoted to production of metallurgical grade alumina. Production facilities are located adjacent to a bauxite reserve or in countries having the largest markets for the product.

Table 5. Alumina Production Capacity

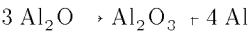
Company	Capacity, 10 t yr
Alcan	4.6
Alcoa	6.5
Alcoa of Australia	2.7
Alusuisse	1.4
Billiton (Royal Dutch Shell Group)	2.1
Conalco (Australia)	1.8
Jamaican government	0.7
Japanese companies	0.3
Kaiser	1.8
Marc Rich	1.0
other government owned facilities ^a	6.3
Pechiney	2.5
Reynolds	2.8
V. A. W. (Germany)	0.7
Total	35.2

^a These are owned by the governments of Argentina, India, Italy, Spain, and others.

The aluminum industry is a cyclic industry responding to global economic activity. The price of metal grade alumina ranged from about \$100 to \$385 t, and spot prices reached \$400 t during certain periods in the 1980s. The largest cost elements in alumina production are bauxite, caustic, energy, and sustaining capital for production equipment. Production costs range from ca \$100 t Al_2O_3 to well over twice that amount, depending on bauxite quality, Bayer plant size, and efficiency. Detailed economic aspects of the bauxite and alumina industries are available (15) as is a broad overview of the economic significance of other aluminum containing compounds (6,16).

Chemical Properties

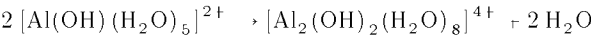
The ground state distribution of electrons in the aluminum atom is $1s^22s^22p\ 3s^23p^1$. The oxidation state of aluminum is +3, except at high temperatures where monovalent species such as AlCl, AlF, and Al_2 have been spectrally identified. At lower temperatures, these compounds disproportionate



Aluminum, although highly electropositive, does not react with water under ordinary conditions because it is protected by a thin (2–3 nm) impervious oxide film that rapidly forms even at room temperature on nascent aluminum surfaces exposed to oxygen. If the protective film is overcome by amalgamation or scratching, water rapidly attacks to form hydrous aluminum oxide. Because of the tendency to amalgamate, aluminum and its alloys

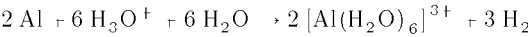
should not be used in contact with mercury or its compounds. Molten aluminum (mp 660°C) is known to react explosively with water (17). Thus the molten metal should not be allowed to touch damp tools or containers.

There is much discussion on the nature of the aluminum species present in slightly acidic and basic solutions. There is general agreement that in solutions below pH 4, the mononuclear Al^{3+} exists coordinated by six water molecules, ie, $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$. The strong positive charge of the Al^{3+} ion polarizes each water molecule and as the pH is increased, a proton is eventually released, forming the monomeric complex ion $[\text{Al}(\text{OH})(\text{H}_2\text{O})_5]^{2+}$. At about pH 5, this complex ion and the hexahydrated Al^{3+} are in equal abundance. The pentahydrate complex ion may dimerize by losing two water molecules

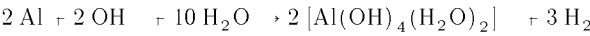


Further deprotonation, dehydration, and polymerization of monomers and dimers may yield ringlike structures of hydroxy–aluminum complexes (10). Coalescence of ring compounds into layers by further growth results in the formation of crystalline aluminum hydroxide at pH 6, the point of minimum aqueous solubility.

Highly purified aluminum, 99.999% Al, is resistant to attack by most acids but can be dissolved in aqua regia or in hydrochloric acid containing a trace of CuCl_2 . Addition of hydrogen peroxide [7722-84-1], H_2O_2 , during dissolution in HCl speeds the process (18). Typical commercial aluminum, 99.85 to 99.95% Al, is soluble in dilute mineral acids but is passivated by concentrated nitric acid. Dissolution in acids is accompanied by evolution of hydrogen and hydration of the aluminum ion

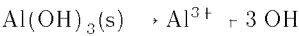


Because of its amphoteric nature, aluminum is also readily attacked by solutions of strong bases. At a pH > 8.5, the solubility of aluminum increases sharply because of the formation and hydration of $\text{Al}(\text{OH})_4^-$ ions

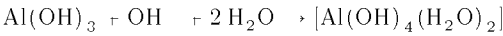
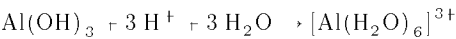


In high caustic Bayer liquor, $\text{Al}(\text{OH})_4^-$ ions exist because there is not enough water to hydrate them.

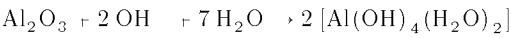
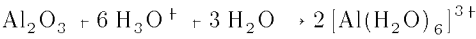
Aluminum hydroxide is capable of reacting as either an acid or a base (18).



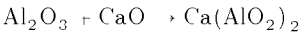
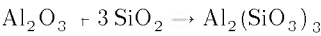
and the hydroxide is readily soluble in both acids and strong bases



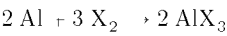
Calcined alumina, $\alpha\text{-Al}_2\text{O}_3$, and naturally occurring corundum are practically insoluble in acids and bases, but partially calcined and low temperature amorphous oxide, such as that which forms on nacent commercial aluminum surfaces, is soluble



The amphoteric nature of the oxide is illustrated by its ability to form silicates and aluminates in the dry state at elevated temperatures



Aluminum also reacts vigorously with the halogens to form trihalides



Commercially Significant Compounds

The aluminum containing compound having the largest worldwide market, estimated to be over 30×10^6 t in 1990, is metal grade alumina. Second, is aluminum hydroxide. In 1990 the market for $\text{Al}(\text{OH})_3$ should approach or exceed 3.5 million metric tons which is equivalent to 2.3 million tons on an alumina basis. The split between additive and feedstock applications for $\text{Al}(\text{OH})_3$ (16) is roughly 50:50. Additive applications include those as flame retardants (qv) in products such as carpets, and to enhance the properties of paper (qv), plastic, polymer, and rubber products. Significant quantities are also used in pharmaceuticals (qv), cosmetics (qv), adhesives (qv), polishes (qv), dentifrices (qv), and glass (qv).

Feedstock applications of $\text{Al}(\text{OH})_3$ for production of other chemicals include almost all of the 5000 plus compounds listed in the CAS registry.

Aluminum Sulfate (Alum). Alum, a double sulfate of potassium and aluminum having twelve waters of crystallization, $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$, is the earliest referenced aluminum containing compound. It was mentioned by Herodotus in the fifth century BC. The Egyptians used alum as a mordant and as a medicine; the Romans used it for fireproofing. Some alums contain sodium or ammonium ions in place of potassium.

Aluminum sulfate, $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$, also known as alum cake, is industrially produced by reaction of $\text{Al}(\text{OH})_3$ and sulfuric acid [7664-93-9], H_2SO_4 , in agitated pressure vessels at about 170°C. The commercial product has about 10% less water of hydration than the theoretical amount. Aluminum sulfate has largely replaced alums for the major applications as a sizing agent in the paper industry and as a coagulant to clarify municipal and industrial water supplies. In terms of worldwide production, it ranks third behind alumina and aluminum hydroxide, with markets in excess of 3×10^6 t yr (19).

Aluminum Halides. All the halogens form covalent aluminum compounds having the formula AlX_3 . The commercially most important are the anhydrous chloride and fluoride, and aluminum chloride hexahydrate.

Anhydrous aluminum chloride, AlCl_3 , is manufactured primarily by reaction of chlorine [7782-50-5] vapor with molten aluminum and used mainly as a catalyst in organic chemistry; ie, in Friedel-Crafts reactions (qv) and in proprietary steps in the production of titanium dioxide [13463-67-7], TiO_2 , pigment. Its manufacture by carbochlorination of alumina or clay is less energy-intensive and is the preferred route for a few producers (19).

Aluminum chloride hexahydrate, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, manufactured from aluminum hydroxide and hydrochloric acid [7647-01-0], HCl, is used in pharmaceuticals and cosmetics as a flocculant and for impregnating textiles. Conversion of solutions of hydrated aluminum chloride with aluminum to the aluminum chlorohydroxy complexes serve as the basis of the most widely used antiperspirant ingredients (20).

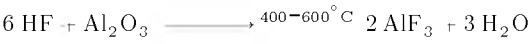
Another cosmetic application of aluminum compounds is as lakes for lipstick manufacture (21). A water-soluble dye can become a lipstick ingredient if combined with compounds that are colorless and insoluble. The result, called a lake, is insoluble in both oil and water. Some dyes are laked with alumina; others are dissolved in water and treated with solutions that precipitate $\text{Al}(\text{OH})_3$ with the dye molecules occluded in the precipitate. These

lakes are mixed with castor oil [8001-79-4] (qv), finely ground, and used as lipstick ingredients.

Aluminum fluoride is important as an additive to the electrolyte of aluminum smelting cells. World production, about 700,000 t yr, is by the hydrofluoric acid [7664-39-3]/HF process and the fluorosilicic acid [16961-83-4], H₂SiF₆, process. In the HF process, acid grade feldspar [7789-75-5], CaF₂, reacts in a rotary kiln with fuming sulfuric acid (oleum) [8014-95-7], H₂SO₄·SO₃, to produce anhydrous HF gas and gypsum (see FLUORINE COMPOUNDS, INORGANIC, HYDROGEN)

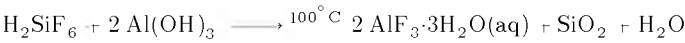


The HF is fed into the bottom stage of a three-stage fluid bed reactor and Al(OH)₃ is fed to the top stage where it is converted to activated alumina at 300–400°C. In the middle stage, rising HF gas contacts downcoming alumina and forms AlF₃



The AlF₃ goes to the bottom stage of the reactor and is removed as product.

In the fluorosilicic acid process, H₂SiF₆ solution, obtained from scrubbing stack gases from phosphate rock fertilizer plants, is reacted with Al(OH)₃ at about 100°C, whereupon silica precipitates and AlF₃ is dissolved.



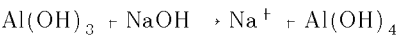
After the SiO₂ is filtered off, the aluminum fluoride is crystallized as the trihydrate which is then calcined at 500–550°C to yield anhydrous AlF₃.

Organoaluminum Compounds. Application of aluminum compounds in organic chemistry came of age in the 1950s when the direct synthesis of trialkylaluminum compounds, particularly triethylaluminum and triisobutylaluminum from metallic aluminum, hydrogen, and the olefins ethylene and isobutylene, made available economic organoaluminum raw materials for a wide variety of chemical reactions (see σ BONDED ALKYLs AND ARYLs).

The alkyls and aryls, R₃Al (in monomer form), are colorless liquids or low melting solids easily oxidized and hydrolyzed when exposed to the atmosphere. Triethylaluminum (TEA), one of the most commercially important members of this family of chemicals, is so reactive it bursts into flame on contact with air, ie, it is pyrophoric, and it reacts violently with water. This behavior is typical and special techniques are necessary for the safe handling and use of organoaluminum compounds.

The alkylaluminum halides, R_nAlX_{3-n}, where X is Cl, Br, I, and R is methyl, ethyl, propyl, iso-butyl, etc, in monomer form, and n = 1 or 2, are less easily oxidized and hydrolyzed than the trialkyls. Organoaluminum hydrides such as diisobutylaluminum hydride [1191-15-7], (iso-C₄H₉)₂AlH, are also available. Organoaluminum compounds are used commercially in multimillion kg yr quantities as catalysts or starting materials for the manufacture of organic compounds such as plastics, elastomers (qv) biodegradable detergents, and organometallics containing zinc, phosphorus, or tin (18,22–24).

Sodium Aluminate. Sodium aluminate is manufactured by dissolving high purity Al(OH)₃ in 50% sodium hydroxide solution



The resulting solutions contain high dissolved solids content in the range of 30 wt % or more. Special surfactant technology (25) is sometimes used to avoid precipitation of Al(OH)₃ or at least to extend the shelf life of the caustic liquor.

Sodium aluminate is used in water purification, in the paper industry, for the after treatment of TiO₂ pigment, and in the manufacture of aluminum containing catalysts and zeolite. Worldwide markets are in the range of 125,000 t yr (19).

Zeolites. A large and growing industrial use of aluminum hydroxide and sodium aluminate is the manufacture of synthetic zeolites (see MOLECULAR SIEVES). Zeolites are aluminosilicates with Si/Al ratios between 1 and infinity. There are 40 natural, and over 100 synthetic, zeolites. All the synthetic structures are made by relatively low (100–150°C) temperature, high pH hydrothermal synthesis. For example the manufacture of the industrially important zeolites A, X, and Y is generally carried out by mixing sodium aluminate and sodium silicate solutions to form a sodium aluminosilicate gel. Gel-aging under hydrothermal conditions crystallizes the final product. In special cases, a small amount of seed crystal is used to control the synthesis.

Zeolite-based materials are extremely versatile: uses include detergent manufacture, ion-exchange resins (ie, water softeners), catalytic applications in the petroleum industry, separation processes (ie, molecular sieves), and as an adsorbent for water, carbon dioxide, mercaptans, and hydrogen sulfide.

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ALUMINATES

Sodium aluminate [1302-42-7], NaAlO₂, has been used as a commercial product since about 1925 when it was introduced as an effective water treatment chemical. Among industrial users of sodium aluminate are producers of paper (qv), paint pigments (qv), silica–alumina or alumina-based catalysts, dishwasher detergents (qv), molecular sieves (qv), concrete, antacids, and others. Sodium aluminate is used in removal of phosphates from municipal and industrial waste waters and for clarification of industrial process and potable water. Commercial sodium aluminate products are available as liquids, and to a lesser degree, in solid form. The formula of anhydrous sodium aluminate is variously given as NaAlO₂ (aluminum sodium oxide [1302-42-7]), Na₂O · Al₂O₃, or Na₂Al₂O₄. Commercial sodium aluminates are not accurately represented by these formulas because the products contain more than the stoichiometric amount of sodium oxide [1313-59-3], Na₂O. The amount of excess caustic in commercial products is indicated by ratios of Na₂O / Al₂O₃ that are typically between 1.05 and 1.15 for dry products, and 1.26 and 1.5 for liquids.

Physical and Chemical Properties

Commercial grades of sodium aluminate contain both waters of hydration and excess sodium hydroxide. In solution, a high pH retards the reversion of sodium aluminate to insoluble aluminum hydroxide. The chemical identity of the soluble species in sodium aluminate solutions has been the focus of much work (1). Solutions of sodium aluminate appear to be totally ionic. The aluminate ion is monovalent and the predominant species present is determined by the Na₂O concentration. The tetrahydroxyaluminate ion [14485-39-3], Al(OH)₄⁻, exists in lower concentrations of caustic; dehydration of Al(OH)₄⁻ to the *meta*-aluminate ion [20653-98-9], AlO₂⁻, is postulated at concentrations of Na₂O above 25%. The formation of polymeric aluminate ions similar to the positively charged polymeric ions formed by hydrolysis of aluminum at low pH does not seem to occur. Al(OH)₄⁻ has been identified as the predominant ion in dilute aluminate solutions (2).

Figure 1 shows a phase equilibrium diagram for soda–alumina–water (3). The point of maximum solubility at 30°C for alumina trihydrate [12252-70-9], Al₂O₃ · 3H₂O, and sodium aluminate is near 23% Al₂O₃ and 20% Na₂O. At higher Na₂O concentrations, the solutions are supersaturated with respect to sodium aluminate; at lower concentrations of Na₂O, the solutions are supersaturated with respect to the trihydrate. At concentrations greater than 23% Al₂O₃ and 20% Na₂O, the solution is supersaturated with respect to both solids. Most commercial solutions are supersaturated with regard to one or both of the solids.

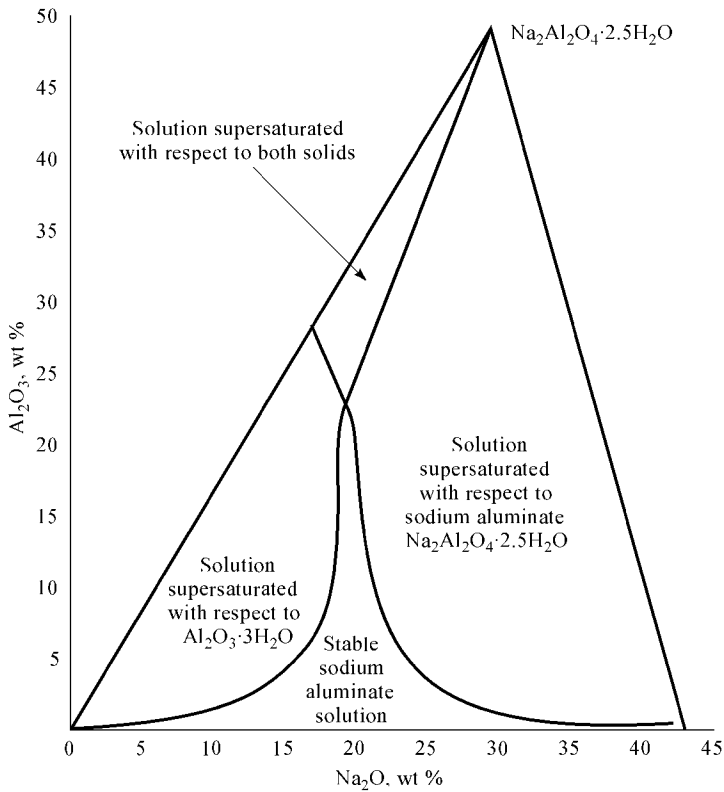


Fig. 1. Equilibrium diagram for the Na₂O–Al₂O₃–H₂O system at 30°C (3).

Manufacture

Small amounts of sodium aluminate are prepared in the lab by fusion of equimolar quantities of sodium carbonate [497-19-8] and aluminum acetate [139-12-8], Al(C₂H₃O₂)₃, at 800°C (4). Other methods involve reaction of sodium hydroxide with amorphous alumina or aluminum [7429-90-5] metal. Commercial quantities of sodium aluminate are made from hydrated alumina, in the form of aluminum hydroxy oxide [24623-77-6], AlO(OH), or aluminum hydroxide [21645-51-2], Al(OH)₃, a product of the Bayer process (5,6) which is used to refine bauxite [1318-16-7], the principal aluminum ore. Commercial grades of sodium aluminate are obtained by digestion of aluminum trihydroxide in aqueous caustic at atmospheric pressure and near the boiling temperature (7). Digestion of the aluminum hydroxy oxide in aqueous sodium hydroxide [1310-73-2] requires pressures of up to 1.38 MPa (13.6 atm) and temperatures of about 200°C. Dry sodium aluminate is obtained by evaporation of water. Several processes for the production of sodium aluminate are known that do not require the addition of water. In one process, bauxite reacts with molten sodium hydroxide at approximately 400°C (8); in

another, aluminum trihydroxide reacts with solid sodium hydroxide (9); additionally, sodium carbonate has been treated with alumina or bauxite in rotary kilns at about 1000°C (10,11). Other similar methods have also been described.

The form of sodium aluminate produced depends upon the manufacturing process. In high temperature, nonaqueous processes, the sodium aluminate product normally contains less than 1% moisture. If a dry product is desired from aqueous digestion processes, some sort of drying operation is required. In practice about half of the digestion liquor is sold as liquid sodium aluminate after filtration and dilution or concentration to conform with product specifications. Some products contain small amounts of powdered insoluble solids that act as precipitation or coagulation aids in water-treatment processes (12). Concentrated solutions of sodium aluminate tend to decompose by precipitation of alumina. Such decomposition is controlled in commercial products by addition of excess caustic and small quantities of certain organic compounds, or stabilizers (7,13–15).

Liquid sodium aluminate is available in steel drums having an approximate capacity of 210 L and bulk shipments are available in either tank trucks or railroad tank cars. The density of liquid sodium aluminate is usually from 1450 to 1510 kg m⁻³. Solid products are available in moisture-proof paper bags or fiber drums containing approximately 23 and 150 kg, respectively.

Economic Aspects

Production figures for sodium aluminate are not released by manufacturers in the United States. There are approximately eight commercial U.S. producers and total production was estimated at 120,000 metric tons in 1990. Prices for large quantities of sodium aluminate are in the range of \$0.22 kg to \$0.43 kg for liquids, depending upon concentration, location, and volume purchased.

Analysis

Commercial liquid sodium aluminates are normally analyzed for total alumina and for sodium oxide by titration with ethylene diaminetetraacetic acid [60-00-4] (EDTA) or hydrochloric acid. Further analysis includes the determination of soluble alumina, soluble silica, total insoluble material, sodium oxide content, and carbon dioxide. Aluminum and sodium can also be determined by emission spectroscopy. The total insoluble material is determined by weighing the ignited residue after extraction of the soluble material with sodium hydroxide. The sodium oxide content is determined in a flame photometer by comparison to proper standards. Carbon dioxide is usually determined by the amount evolved, as in the Underwood method.

The determination of the soluble or available sodium aluminate presents difficulties because sodium aluminate begins to hydrolyze to the insoluble alumina trihydrate in water. The degree of hydrolysis depends on concentration, temperature, and time. It is therefore necessary to use a method of analysis that simultaneously affords control of the hydrolysis and gives the amount of available sodium aluminate encountered. This is best done by extracting the soluble alumina using sodium hydroxide solutions and subsequently determining the alumina content by gravimetric methods or titration with EDTA or hydrochloric acid (16).

Uses

Sodium aluminate is used in the treatment of industrial and municipal water supplies and the use of sodium aluminate is approved in the clarification of drinking water. The FDA approves the use of sodium aluminate in steam generation systems where the steam contacts food. One early use of sodium aluminate was in lime softening processes, where it increases the precipitation of ions contributing to hardness and improves suspended solids removal from the treated water (17). Sodium aluminate reacts with silica to leave very low residual concentrations of silica in hot process water softeners. Sodium aluminate is often used with other chemicals such as alum, ferric salts, clays, and polyelectrolytes, as a coagulant aid (18,19).

Sodium aluminate is an effective precipitant for soluble phosphate in sewage and is especially useful in wastewater having low alkalinity (20,21). Sodium aluminate hydrolyzes in water to Al(OH)₃ and Al⁺³ which precipitate soluble phosphate as aluminum phosphate [7784-30-7], AlPO₄. Sodium aluminate has also been described as an effective aid for the removal of fluorides from some industrial waste waters (22). Combinations of sodium aluminate and other chemicals are being used to improve the detackification of paint particles in water from spray-painting operations (23).

Large quantities of sodium aluminate are used in papermaking where it improves sizing, filler retention, and pitch deposition (24–28). The addition of sodium aluminate to titanium dioxide paint pigment improves the nonchalking performance of outdoor paints (29,30). The etching of glass (qv) and ceramics (qv) by alkaline washing solutions is inhibited by inclusion of sodium aluminate in the formulations (31,32). The use of sodium aluminate solutions in the processing of acrylic and polyester synthetic fibers improves drying, antipiling, and antistatic properties of the fibers (33,34).

The recovery of sand from foundry molds and cores is much easier when binders made water soluble by use of sodium aluminate are used in place of insoluble resin binders (35,36). Sodium aluminate acts as a setting accelerator for Portland cement (qv) (37). In similar application, addition to concrete provides a longer gel time before fully curing (38).

One application patented in 1989 is the injection of sodium aluminate into silica-containing formations for enhanced petroleum recovery (39). Additionally, the pharmaceutical industry uses sodium aluminate as an alkaline source of aluminum for the production of certain antacids (40).

Sodium aluminate is widely used in the preparation of alumina-based catalysts. Aluminosilicate [1327-36-2] can be prepared by impregnating silica gel with alumina obtained from sodium aluminate and aluminum sulfate (41,42). Reaction of sodium aluminate with silica or silicates has produced porous crystalline aluminosilicates which are useful as adsorbents and catalyst support materials, ie, molecular sieves (qv) (43,44).

One method for using sodium aluminate to desulfurize flue gas containing sulfur dioxide is described (45). This procedure led to a process where aluminum sulfate [10043-01-3] could be generated as a by-product of flue gas desulfurization (46).

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ALUMINUM CARBOXYLATES

Aluminum salts of carboxylic acids, aluminum carboxylates, may occur as aluminum tricarboxylates (normal aluminum carboxylates), $\text{Al}(\text{OOCR})_3$; monohydroxy (monobasic) aluminum dicarboxylates, $(\text{RCOO})_2\text{Al}(\text{OH})$; and dihydroxy (dibasic) aluminum monocarboxylates, $\text{RCOOAl}(\text{OH})_2$. Aluminum carboxylates are used in three general areas: textiles, gelling, and pharmaceuticals. Derivatives of low molecular weight carboxylic acids have been mainly associated with textile applications; those of fatty carboxylic acids are associated with gelling salts; and more complex carboxylates find applications in pharmaceuticals.

The development of new aluminum carboxylates is evident in the literature. However, sales volume has decreased or the number of suppliers has been concentrated to such an extent that the U.S. International Trade Commission now reports data only for aluminum tristearate (867 t at \$1.34/kg) (1). The aluminum carboxylates of most commercial interest according to the trade literature (2,3) are given in Table 1.

Table 1. Commercially Important Aluminum Carboxylates

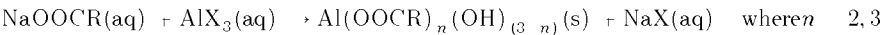
Name	CASRegistryNumber	Empiricalformula	Molwt	Mp, °C
monobasic aluminum formate	[51575-25-8]	$\text{C}_2\text{H}_3\text{AlO}_5$	134.02	
normal aluminum formate	[7360-53-4]	$\text{C}_3\text{H}_3\text{AlO}$	162.03	
monobasic aluminum acetate	[142-03-0]	$\text{C}_4\text{H}_7\text{AlO}_5$	162.08	54
normal aluminum acetate	[139-12-8]	$\text{C}_4\text{H}_9\text{AlO}$	204.09	
dihydroxyaluminum aminoacetate	[13682-92-3]	$\text{C}_2\text{H}_7\text{AlNO}_4$	135.06	
dihydroxyaluminum aminoacetate hydrate	[41354-58-7]	$\text{C}_2\text{H}_7\text{AlNO}_4 \cdot x\text{H}_2\text{O}$		
aluminum octanoate	[30745-55-2]	$\text{C}_{18}\text{H}_{31}\text{AlO}_5$	474.4	
aluminum 2-ethylhexanoate	[6028-57-5]	$\text{C}_{18}\text{H}_{31}\text{AlO}_5$	474.4	
aluminum monostearate	[7047-84-9]	$\text{C}_{18}\text{H}_{37}\text{AlO}_4$	344.5	155
aluminum distearate	[300-92-5]	$\text{C}_{36}\text{H}_{71}\text{AlO}_5$	610.9	145
aluminum tristearate	[637-12-7]	$\text{C}_{54}\text{H}_{106}\text{AlO}$	877.4	115

Aluminum Salts of Low Molecular Weight Carboxylic Acids

Monobasic aluminum acetate (eg, aluminum subacetate), aluminum formoacetate, normal aluminum formate, and basic aluminum formate have found widespread use as mordants in dyeing, in the formulation of waterproofing compositions for textiles, and for dermatological treatment.

Monobasic aluminum acetate, $\text{HOAl}(\text{OOCCH}_3)_2$, the most commercially significant of the low molecular weight salts, is available as a fine white powder stabilized with boric acid. It is soluble in water and insoluble in most organic solvents (4). Although it has been prepared from aluminum chloride hexahydrate and sodium acetate (5), the commercial method involves the reaction of metallic aluminum and aqueous acetic acid containing a small amount of boric acid stabilizer. Mercury chloride can be used as a catalyst (6). The resulting solution is filtered and spray dried. The energetics of the aluminum soap formation seems to be dominated by the chemistry of the carboxyl and solvated metal ions. Controlled decomposition of a variety of aluminum carboxylates has been carried out at different rates in different atmospheres. Hydroxyl stoichiometry can be controlled by water content to make $\text{Al}(\text{OH})_n(\text{OOCCH}_3)_{3-n}$ (7–9).

The greatest industrial consumption of monobasic aluminum acetate has been as a solution in the preparation of red color lakes for the dyeing of cotton. Formation of a water-resistant coating on fabrics, paper, leather, or other materials is also an important application. In this process, for example, cloth is dipped into a solution of water-soluble soap, then into the aluminum salt solution, forming an insoluble, water-resistant aluminum soap coating on the fiber surfaces (10).



Freshly prepared aluminum subacetate is also used to cross-link acid-hydrolyzed, collagen-derived protein. This procedure is useful in the food, pharmaceutical, and photographic industries (11).

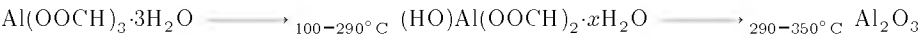
Monobasic aluminum acetate is dispensed as a 7% aqueous solution for the topical treatment of certain dermatological conditions, where a combination of detergent, antiseptic, astringent, and heat-dispersant effects are needed (12). The solution, diluted with 20–40 parts water, is applied topically to the skin and mucous membranes as a wet dressing (13). Burrow's solution, prepared from aluminum subacetate solution by the addition of a specific amount of acetic acid, is also used as a topical wet dressing. Standards of purity and concentration have been established for both pharmaceutical aluminum acetate solutions (13). Each 100 mL of aluminum subacetate solution yields 2.30–2.60 g of aluminum oxide and 5.43–6.13 g of acetic acid upon hydrolysis. For the Burow's solution, each 100 mL yields 1.20–1.45 g of aluminum oxide and 4.25–5.12 g of acetic acid. Both solutions may be stabilized to hydrolysis by the addition of boric acid in amounts not to exceed 0.9% and 0.6% for the subacetate and Burow's solutions, respectively (13).

Aluminum diacetate is used as a nucleating agent with crystalline polypropylene to improve the efficiency of reproducing lightweight printing plates having high dimensional stability and superior printing characteristics (14). It is also used as an esterification catalyst: 2,6-naphthalenedicarboxylic acid and methanol are converted to the dimethyl ester (82.5%) in one hour at 220°C (15). Dibasic aluminum monoacetate [7360-44-3], $(\text{HO})_2\text{Al}(\text{OOCCH}_3)$, is an essential feature in formaldehyde-free durable press finishing by the glyoxal-glycol process. It is a heat stabilizer acting to suppress tendering and yellowing during curing (16).

Production of both monobasic aluminum diformate, $(\text{HO})\text{Al}(\text{OOCH})_2$, and monobasic aluminum formoacetate, $(\text{HO})\text{Al}(\text{OOCH})(\text{OOCCH}_3)$, has declined. One reason could be the ready substitution of inexpensive aluminum formate solution (17–19) for solid aluminum acetate in formoacetate in most of the common commercial applications. Monobasic aluminum formoacetate, mol wt 148.05, mp 350°C, is a fine crystalline powder, prepared from aluminum metal. It is used for fabric water repellency and in the tanning of collagen tape for surgical sutures (10).

Aluminum triformate [7360-53-4], commercially available as a white crystalline powder, appears amorphous under the microscope. Its solubility in cold water is very low, rising to nearly 25% in boiling water (pH 3.2). It remains in solution in a highly saturated state. Infrared analysis of solid aluminum

triformate suggests that both oxygen atoms of the formate ion are coordinated to the aluminum, giving a coordination number of six (20). Aluminum chloride, isopropoxide, or hydrate reacts with 98% formic acid (21,22) to yield a mixture of aluminum formates plus their hydrates in a highly supersaturated solution. When excess formic acid is added, the triformate crystallizes after standing for a day (23). Aluminum formate is formulated as Al(OOCH)₃·HCOOH (24). Aluminum triformate trihydrate can be made from AlCl₃ and sodium formate or from formic acid plus freshly prepared Al(OH)₃. At 100°C this product is hydrolyzed to the monobasic formate. Decomposition to the monobasic formate also occurs at <290°C, going then to alumina at 350°C (25), as shown



Most commercial aluminum formate is monobasic aluminum diformate because of the difficulties involved in triformate preparation. The main application is in textile waterproofing. Aluminum formate reacts with casein to form a water-soluble complex, which can emulsify paraffin and certain other waxes. Fabrics immersed in these emulsions are rendered water repellent (26–28).

Aluminum Salts of Higher Molecular Weight Fatty Acids

This group of aluminum carboxylates is characterized mainly by its ability to gel vegetable oils and hydrocarbons. Again, monocarboxylate, dicarboxylate, and tricarboxylate salts are important. The chemical, physical, and biological properties of the various types of aluminum stearates have been reviewed (29). Other products include aluminum palmitate and aluminum 2-ethylhexanoate (30).

Dihydroxyaluminum monostearate, (HO)₂Al(OOC(CH₂)₁₇CH₃), is a fine white to yellowish-white powder with a faint characteristic odor and low toxicity. This salt melts at 155°C and is insoluble in water, alcohol, and ether (31). It is prepared by treating an aqueous solution of chlorodihydroxyaluminum with a solution of sodium stearate (32). USP dihydroxyaluminum stearate assays between 14.5 and 16.5% alumina (31), partly because it contains a mixture of stearate and palmitate.

Aluminum monostearate has been used in the pharmaceutical industry as a gelling agent for penicillin G procaine (31), as a virus vaccine adjuvant (32), in long-lasting depot-injectable formulations (33), and for prolonged somatotropin release to enhance lactation in dairy cattle (34). It is also used with adrenocorticotrophic hormone (ACTH) peptides for injection (35), for acid release (36), and for dispersion of suppository ingredients (37,38). Aluminum monostearate has been used in the preparation of synthetic greases (39), in water-repellent formulations (40), for fiber lubrication with improved dye receptivity for polyolefins (41), to improve melt and heat resistance of polyesters (42), and as an aqueous-based spray-on mold-release agent for urethane-bound particle board (43).

Monohydroxyaluminum distearate, (HO)Al(OOC(CH₂)₁₇CH₃)₂, used to be the largest selling aluminum carboxylate (1). Although still sold, the product is no longer listed in the U.S. International Trade Commission Report (1) because of low volume or confidentiality constraints because of too few suppliers. Aluminum distearate is a white powder that is insoluble in water, alcohol, and ether. A key property is its ability to gel vegetable oils and hydrocarbons. Aluminum distearate is prepared by the reaction of aqueous sodium stearate with aqueous aluminum sulfate or chloride at pH 7.3. Aluminum monostearate is formed if the sodium stearate solution is held at pH 9.5 (44).

Gels made from aluminum distearate (and some other carboxylate analogues) have more body than those made from other metals; the aluminum gels also show marked thixotropic properties. Aluminum distearate has been used in cosmetics formulas (45–47) (see COSMETICS) (48,49), as a thickener in grease (50–52), as a gasoline additive for combustion efficiency (53) or gelation (54), as a coating additive (55–57) and a polymer additive to enhance dyeability and weatherability (58), as a salt-bridge-type cross-linker (59), and as a mold-release agent (60).

Aluminum tristearate, Al(OOC(CH₂)₁₇CH₃)₃, is available as a hard, white, technical-grade solid. It is insoluble in water, alcohol, and ether, forming gels with vegetable oils and hydrocarbons (61). High quality aluminum tristearate is made by reaction of aluminum isopropoxide [551-31-7] and stearic acid in anhydrous pyridine; the product precipitates as a pyridine complex. Infrared analysis indicates that no hydroxyl remains after the pyridine is removed under vacuum (62). Applications for aluminum tristearate include cosmetic gels (45), pharmaceutical additives (63,64), polymer additives (65,66), grease additives (67,68), toner adjuvants (69), antifoam agents (70), rocket-fuel and explosives additives (71,72), and waterproofing agents (40,72).

Other aluminum fatty carboxylates have been used to a lesser degree. Hydroxyaluminum dilaurate is used in agricultural feed to optimize digestion (73) and as a liquid petroleum grease thickener (74). Aluminum palmitate [14236-50-1], C₃₂H₆₃AlO₅, is used as a gelling agent in rocket propellents and in ointment bases for polyolefin dyeing (65,75). Aluminum (stearate-myristate) has been used as an acid catalyst scavenger during polypropylene manufacture (76), whereas aluminum "octoate" (aluminum 2-ethylhexanoate) [6028-57-5], has been used as a gasoline gellant (77,78).

Aluminum Salts of More Complex Carboxylic Acids

The aluminum salts of drugs are significant for two principal reasons: reduction of drug acidity in the stomach lining and reduction of undesirable flavor. Examples are the aluminum salts of glycine, acetylsalicylic acid, ibuprofen, flurbiprofen, fenoprofen, flufenamic acid, oxaprozin, and a variety of aminobenzoic acid. Some of these compounds are listed in Table 2.

Table 2. Aluminum Carboxylates Used as Pharmaceuticals

Name	CASRegistryNumber	Empiricalformula	Molwt
monohydroxyaluminum glycinate	[13682-92-3]	C ₂ H ₄ AlNO ₄	135.06
monohydroxyaluminum acetylsalicylate	[23413-80-1]	C ₁₈ H ₁₅ AlO ₉	402.3
monohydroxyaluminum ibuprofen	[61054-06-6]	C ₂₃ H ₃₅ AlO ₅	454.5
dihydroxyaluminum ibuprofen	[63649-76-3]	C ₁₃ H ₁₉ AlO ₄	266.3
monohydroxyaluminum fenoprofen	[58348-96-2]	C ₂₀ H ₂₇ AlO ₇	526.5
dihydroxyaluminum fenoprofen	[58348-95-1]	C ₁₅ H ₁₅ AlO ₅	302.3
aluminum flufenamate	[16449-54-0]	C ₄₂ H ₂₇ AlF ₉ N ₃ O	867.6

Dihydroxyaluminum aminoacetate (aluminum glycinate), a white, odorless powder with a faintly sweet taste, is insoluble in water and organic solvents. It is made by the reaction of aluminum isopropoxide with glycine, HOOCCH₂NH₂, in aqueous solution (79) or by reaction of aluminum chloride in methanol with aqueous sodium glycinate (80). Upon drying, moisture loss of the hydrated product cannot exceed 14.5% (81). Aluminum oxide assay yields 35.5–38.5%. Because dihydroxyaluminum aminoacetate gives a pH of 6.5–7.5 when suspended in water (81), it provides prompt buffering in the biologically ideal pH range, affording consistent neutralization. This action minimizes pain and promotes healing (see GASTROINTESTINAL AGENTS). It is thus useful for treatment of gastritis and hyperacidity (82).

Aluminum acetylsalicylate is a tasteless, nonbasic, stable, alternative therapeutic salt to aspirin (83). Also called aluminum aspirin, it is an insoluble white to off-white powder prepared by reaction of aluminum isopropoxide with sodium acetylsalicylate in an organic solvent. The product precipitates from the reaction mixture (83). Standards require that aluminum aspirin contain not less than the equivalent of 80% aspirin, corresponding to 90% purity on an anhydrous basis. The aluminum oxide assay must be 12–17% (81).

Analgesic and antipyretic ibuprofen, 2-(*p*-isobutylphenyl)propionic acid, is converted to its monohydroxyaluminum salt by converting the acid to its sodium salt using dilute caustic, followed by concurrent addition of equimolar amounts of aluminum nitrate and sodium bicarbonate (84). This salt can also

be prepared by reaction of aluminum chloride with the sodium salt of ibuprofen at 18°C and pH 7.1–7.3 (85). The dibasic aluminum salt must be made under different conditions (86). The monobasic aluminum salt has a more pleasant taste than either the parent acid or the more basic salt (84). The aluminum salts are useful for preventing scar tissue (3) and in the treatment of *Herpes simplex* I and II infections (87). Aspirin, acetaminophen, and phenacetin behave synergistically with ibuprofen aluminum salts with respect to anti-inflammatory and analgesic response (88,89).

Fenoprofen, 2-(3-phenoxyphenyl)propionic acid, is made into its monohydroxyaluminum or dihydroxyaluminum salt by reaction of the sodium salt of the acid with aluminum nitrate or chloride under pH control (90,91). The aluminum salt, which is hydrolyzed in the stomach, is more palatable for arthritis treatment (92,93).

Aluminum flufenamate, tris-[2-(3-trifluoromethylphenyl)aminobenzoate]aluminum, is a safer and more effective analgesic than aspirin (94). The dihydroxyaluminum flufenamate is made by reaction of flufenamic acid with aqueous caustic, followed by addition of aluminum chloride with stirring at 42°C for 15 min to give 99% yield (95). Both forms are less irritating and less toxic than the parent acid or aspirin (94,95).

The anti-inflammatory agent Oxaprozin, 2-(4,5-diphenyl-2-oxazole)propionic acid monoaluminum and dihydroxyaluminum salts, is made by reaction of the sodium salt with aluminum sulfate under controlled conditions (96). Again, the aluminum salts of many carboxylic acid based drugs are less irritating, ulcerous, and or toxic, and have a more pleasant taste than their parent acids.

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ALUMINUM HALIDES AND ALUMINUM NITRATE

The aluminum halides and aluminum nitrates have similar properties with the exception of the family of aluminum fluoride compounds which are discussed elsewhere (see FLUORINE COMPOUNDS, INORGANIC). Of the remaining members in this aluminum halide family, chloride derivatives are the most commercially important; aluminum bromide [7727-15-3] AlBr_3 , aluminum iodide [7784-23-8], AlI_3 , and aluminum nitrate [13473-90-0], $\text{Al}(\text{NO}_3)_3$, are of only minor commercial interest.

ALUMINUM CHLORIDE

The chemistry of aluminum chloride is influenced significantly by hydration. Aluminum chloride hexahydrate [7784-13-6], $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, is a crystalline solid that dissolves easily in water forming ionic species. Heating the hydrate results in the loss of hydrogen chloride [7647-01-0], HCl , and formation of aluminum oxide [1344-28-1], Al_2O_3 . On the other hand, anhydrous aluminum chloride [7466-70-0] reacts violently with water evolving heat, a gas consisting of hydrogen chloride and steam, and aluminum oxide particulates. Anhydrous aluminum chloride sublimates at 180°C leaving no residue. The uses of anhydrous aluminum chloride and the hydrated form are also very different. The anhydrous material is a Lewis acid used as an alkylation catalyst. The hydrate is used principally as a flocculating aid.

Commercially, aluminum chloride is available as the anhydrous AlCl_3 , as the hexahydrate, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, or as a 28% aqueous solution designated 32°Be'. Polyaluminum chloride, or poly(aluminum hydroxy) chloride [1327-41-9] is a member of the family of basic aluminum chlorides. These are partially neutralized hydrates having the formula $\text{Al}_2\text{Cl}_{6-x}(\text{OH})_x \cdot 6\text{H}_2\text{O}$ where $x = 1-5$.

Anhydrous Aluminum Chloride

Properties. Anhydrous aluminum chloride is a hygroscopic, white solid that reacts with moisture in air. Properties are shown in Table 1. Commercial grades vary in color from light yellow to light gray as a result of impurities. Crystal size is dependent upon method of manufacture. At atmospheric pressure, anhydrous aluminum chloride sublimates at 180°C as the dimer [13845-12-0], Al_2Cl_6 , which dissociates to the monomer beginning at approximately 300°C . Dissociation is essentially complete at 1100°C . As can be seen from Figure 1, the liquid form of aluminum chloride exists only at elevated temperatures and pressures.

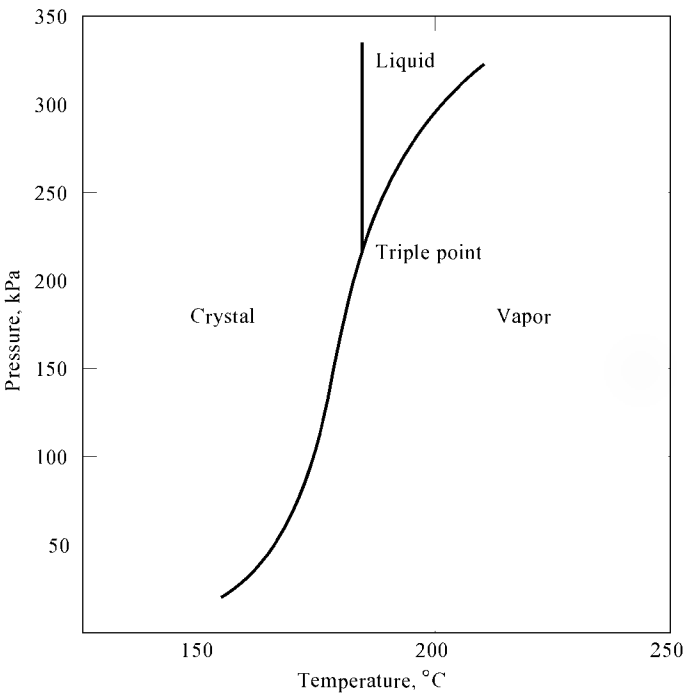


Fig. 1. Aluminum chloride phase diagram. The triple point occurs at 192.5°C at 33 kPa. To convert to psi, multiply by 0.145.

Table 1. Physical Properties of Anhydrous Aluminum Chloride^a

Property	Value
molecular weight	133.34054
density at 25°C^b , g/mL	2.46
sublimation temperature ^b , $^\circ\text{C}$	180.2
triple point, $^\circ\text{C}$, 233 kPa ^c	192.5 ± 0.2
heat of formation, 25°C , kJ/mol ^d	-705.63 ± 0.84
heat of sublimation of dimer, 25°C , kJ/mol ^d	115.52 ± 2.3
heat of solution, 20°C , kJ/mol ^d	-329.1
heat of fusion, kJ/mol ^d	35.35 ± 0.84
entropy, 25°C , J/(K·mol) ^d	109.29 ± 0.42

heat capacity, 25°C, J (K·mol)^d

91.128

^a Ref. 1.

^b Ref. 2.

^c To convert kPa to psi, multiply by 0.145.

^d To convert J to cal, divide by 4.184.

Aluminum chloride dissolves readily in chlorinated solvents such as chloroform, methylene chloride, and carbon tetrachloride. In polar aprotic solvents, such as acetonitrile, ethyl ether, anisole, nitromethane, and nitrobenzene, it dissolves forming a complex with the solvent. The catalytic activity of aluminum chloride is moderated by these complexes. Anhydrous aluminum chloride reacts vigorously with most protic solvents, such as water and alcohols. The ability to catalyze alkylation reactions is lost by complexing aluminum chloride with these protic solvents. However, small amounts of these "procatalysts" can promote the formation of catalytically active aluminum chloride complexes.

Manufacture. In the United States anhydrous aluminum chloride is manufactured by the exothermic reaction of chlorine [7782-50-5], Cl₂, vapor with molten aluminum [7429-90-5]. The aluminum may be scrap, secondary ingot of varying purity, or prime ingot. Melting of additional metal feed, external cooling of the reactor, and regulation of the chlorine feed rate, control the reactor temperature between 600–750°C. Chlorine is fed into the molten aluminum pool below the pool's surface. Aluminum chloride sublimes out of the pool and into a condensing vessel where the product solidifies on the condenser walls. Condensers are normally air-cooled, thin-walled steel vertical cylinders having cone-shaped bottoms. The aluminum chloride grows into teardrop-shaped crystals which are periodically removed, crushed, screened, and packaged under a dry air or nitrogen atmosphere. The product may be colored yellow because of the presence of excess chlorine or ferric chloride [7705-08-0]. A gray or greenish coloration indicates the presence of condensed aluminum vapor in the product.

The chlorination of aluminous materials in the production of aluminum chloride has been thoroughly investigated (2). The Gulf Oil Company produced aluminum chloride from calcined bauxite [1318-16-7] and coke from 1920 to 1960 (3).

In 1948 BASF commercialized the process of catalytic chlorination of gamma-alumina in a fluidized bed (4). This process is still used in Germany. A mixture of chlorine and carbon monoxide passes over a beechwood charcoal catalyst in a preliminary step which partially converts the gases to phosgene. The hot gas mixture enters the bottom of a lined reactor and as the gas flows upward through a bed of finely divided particles of gamma-alumina, aluminum chloride gas forms. Catalytic amounts of sodium chloride are added to maintain a liquid phase within the fluidized bed of alumina and promote the conversion of the solid gamma-alumina to aluminum chloride vapor. Finely divided droplets of molten sodium aluminum chloride develop under these reaction conditions. The hot gas which exits the top of the reactor is filtered to remove entrained liquids and solids. The anhydrous aluminum chloride solidifies in a condenser, is collected, and packaged. Off-gases are purified before recycling.

The hot (400–500°C) inlet gases warm the alumina particles and the mildly exothermic reaction serves to maintain the heat of the furnace between 500 and 600°C. The alumina particle size is critical for maintaining a good reaction rate and a fluidized bed.

The main impurities of the reaction product are iron (0.02 to 0.03%) and small quantities of sodium (<0.01%) as chlorides. No chlorine-consuming side reactions occur and the product requires only one step to obtain a product free of significant impurities. The lower process temperatures also reduce demands on the materials of plant construction and maintenance.

Both the Toth and Alcoa processes provide aluminum chloride for subsequent reduction to aluminum. Pilot-plant tests of these processes have shown difficulties exist in producing aluminum chloride of the purity needed. In the Toth process for the production of aluminum chloride, kaolin [1332-58-7] clay is used as the source of alumina (5). The clay is mixed with sulfur and carbon, and the mixture is ground together, pelletized, and calcined at 700°C. The calcined mixture is chlorinated at 800°C and gaseous aluminum chloride is evolved. The clay used contains considerable amounts of silica, titania, and iron oxides, which chlorinate and must be separated. Silicon tetrachloride and titanium tetrachloride are separated by distillation. Resublimation of aluminum chloride is required to reduce contamination from iron chloride.

In the Alcoa process, high purity aluminum chloride is prepared for electrolytic reduction to aluminum (6). The starting material is Bayer process alumina. A small amount of sodium compounds (2.0–0.5% as Na₂O) is added to facilitate alumina chlorination. This alumina is coked or impregnated with carbon to yield a product containing 15–24 wt % carbon and the coked alumina, contaminated with sodium but otherwise substantially free of elements yielding volatile chlorides, reacts with chlorine in a fluidized-bed reactor. Reaction temperature is controlled preferably at about 600°C. Effluent gases from the reactor are cooled below the reaction temperature, but above the condensation temperature of aluminum chloride, and filtered. Solids consisting of aluminum oxide, carbon dust, aluminum oxychloride [13596-11-7], AlOCl, and a liquid composed of equimolar quantities of sodium and aluminum chlorides are removed from the gas stream. Material retained on the filter is returned in controlled amounts to the reactor to improve the efficiency of operation. After filtration, the gas stream containing essentially pure aluminum chloride and oxides of carbon is conducted to a desublimer (7). The aluminum chloride vapor can be condensed on solid particles of aluminum chloride maintained in a temperature-controlled fluidized bed (8). Product condensed in this manner is a lobular, free-flowing powder suitable for electrolytic reduction to aluminum. Traces of chlorinated biphenyls and phosgene contaminate aluminum chloride produced in this manner, making this product unsuitable for most commercial aluminum chloride applications.

Economic Aspects. The North American demand for anhydrous aluminum chloride, estimated to be from 25,000 to 30,000 metric tons per year (9), is divided among the applications shown in Figure 2. In 1984 the anhydrous aluminum chloride demand was estimated at 40,000 tons in Western Europe and 9,000 tons in Japan (10). Pricing is heavily dependent on the cost of aluminum metal. The delivered price of aluminum chloride during the first quarter of 1989 ranged from \$0.32/kg for bulk truckloads to \$0.35/kg for small drums. The North American demand for this catalyst has remained relatively constant over the last 20 years (10).

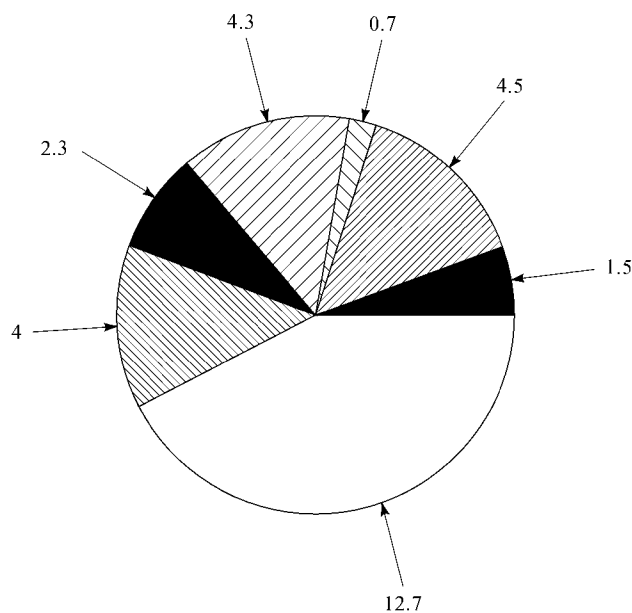


Fig. 2. Annual anhydrous aluminum chloride market, 1984, 10³ t/yr (10). ■, Dyestuffs; ▨, ethylbenzene; ▩, ethyl chloride; ▤, hydrocarbon resin; ▦, pharmaceuticals; ▧, titanium dioxide; and □, other applications.

Specifications and Packaging. Aluminum chloride's catalytic activity depends on its purity and particle size. Moisture contamination is an important concern and exposure to humid air must be prevented to preserve product integrity. Moisture contamination can be determined by a sample's nonvolatile material content. After subliming, the material remaining is principally nonvolatile aluminum oxide. Water contamination leads to a higher content of nonvolatile material.

In many chemical processes the catalyst particle size is important. The smaller the aluminum chloride particles, the faster it dissolves in reaction solvents. Particle-size distribution is controlled in the manufacturer's screening process. Typical properties of a commercial powder are shown in Table 2.

Table 2. Properties of Commercial Anhydrous Aluminum Chloride^a

Property	Value
mesh size, U.S. sieve series	20 ^b
nonvolatile material, %	0.15
aluminum chloride, %	99.6
water insolubles, ppm	150
free aluminum, ppm	30
iron, ppm	30
magnesium, ppm	5

^a Ref. 11.
^b Corresponds to pore size of 840 μm.

Aluminum chloride is available in a wide variety of moisture-free packages. Pails and drums are often used when fixed amounts of aluminum chloride are required for batch operations. For small operations, bags having a specially designed liner to maintain moisture-free product are available. For shipments from 200 to 1200 kilograms net, suppliers offer 37.8, 75.7, 113.6, and 208-L drums. Semibulk bins hold up to 11,000 kilograms net. These returnable containers are constructed of fiberglass to make shipping, storage, and handling of aluminum chloride more convenient. Aluminum chloride can also be purchased in bulk truck trailers in quantity up to 90,000 kg net (11).

Safety and Handling. Anhydrous aluminum chloride reacts with water or moisture, generating heat, steam, and hydrochloric acid vapors. Product containers should be stored inside a cool, dry, well-ventilated area and bulk handling systems must be waterproofed; the product transferred only in a nitrogen or dry air system. Although aluminum chloride is nonflammable, it should also be stored away from combustible materials. In storage, some reaction with moisture may occur and over time can lead to a pressure build-up from HCl in the container. Containers should be carefully vented before being opened (11). Safety goggles or face shields, rubber gloves, rubber shoes, and coveralls made of acid-resistant material should be used in handling. A NIOSH OSHA-certified respirator is also required to prevent breathing fumes and dust (11). Aluminum chloride reacts with moisture in the skin, in the eyes, ears, nose, and throat (11).

Environmental Protection. Fumes resulting from exposure of anhydrous aluminum chloride to moisture are corrosive and acidic. Collection systems should be provided to conduct aluminum chloride dusts or gases to a scrubbing device. The choice of equipment, usually one of economics, ranges from simple packed-tower scrubbers to sophisticated high energy devices such as those of a Venturi design (11).

Spills should be picked up before flushing thoroughly with water and neutralizing with soda ash or lime. The introduction of aluminum chloride into any drainage system results in the reduction of effluent pH, which can be adjusted using caustic soda or lime (11).

Uses. Aluminum chloride is used as a catalyst in a wide variety of manufacturing processes, such as the polymerization of light molecular weight hydrocarbons in the manufacture of hydrocarbon resins. Friedel-Crafts reactions (qv) which employ this catalyst are used extensively in the synthesis of agricultural chemicals, pharmaceuticals (qv), detergents, and dyes (12).

Aluminum chloride is a nucleating agent in the production of titanium dioxide [13463-67-7] (rutile) used as a white pigment in a variety of paints, paper, and plastics. In the manufacture of titanium dioxide (13), aluminum chloride is mixed with titanium tetrachloride to ensure the formation of the rutile crystalline structure during the reaction with oxygen at 1300–1450°C (see TITANIUM COMPOUNDS). Sufficient aluminum chloride is used to produce TiO₂ containing 1% Al₂O₃. The pigment is wet treated, filtered, washed, dried, and fluid-energy-milled to form a dry TiO₂ for plastic pigmentation and for paints. Environmental and cost problems have favored use of this chloride process.

Aluminum Chloride Hexahydrate

The hexahydrate of aluminum chloride is a deliquescent, crystalline solid soluble in water and alcohol and usually made by dissolving aluminum hydroxide [21645-51-2], Al(OH)₃, in concentrated hydrochloric acid. When the acid is depleted, the solution is cooled to 0°C and gaseous hydrogen chloride is introduced. Crystalline aluminum chloride hexahydrate, AlCl₃·6H₂O, is precipitated, filtered from the liquor, washed with ethyl ether, and dried.

Alternatively, anhydrous aluminum chloride may be hydrolyzed in chilled dilute hydrochloric acid. Briquetting of the anhydrous material slows the reaction and the hydrogen chloride evolved may be recycled to aid precipitation of the hexahydrate.

Aluminum chloride hexahydrate is available in a 28° by weight (32° Be') aqueous solution shipped in glass carboys, tank cars, or trucks. Crystalline hexahydrate is shipped in glass containers or plastic-lined drums. In 1980, 5200 metric tons of aluminum chloride hexahydrate on a 100° AlCl₃ basis was produced in the United States (10).

Roofing granules and mineral aggregate for bituminous products are treated with aluminum chloride solution to improve adhesion of the asphalt (14) (see BUILDING MATERIALS, SURVEY). Pigmented coatings (qv), containing sodium silicate, Na₂SiO₃, and used to color roofing granules, are insolubilized by spraying with aluminum chloride solution and then heating. Aluminum chloride hydrates are the alumina sources used in the manufacture of special forms of alumina and alumina–silica refractories (qv) such as alumina fibers (15), finely dispersed alumina for pesticide carriers (16), and catalyst substrates. Certain casting molds are hardened by spraying with a solution of aluminum chloride before firing.

Aluminum chloride hydrate is used in textile finishing to impart crease recovery and nonyellowing properties to cotton (qv) fabrics, antistatic characteristics to polyester, polyimide, and acrylic fabrics, and to improve the flammability rating of nylon (see TEXTILES). Dye-bleeding of printed textile may be blocked (17) by treatment with aluminum chloride and zinc acetate, Zn(O₂CCH₃)₂, followed by solubilizing with ethylenediamine tetraacetic acid, and washing from the fabric.

Basic Aluminum Chlorides

The class of compounds identified as basic aluminum chlorides [1327-41-9] is used primarily in deoderant, antiperspirant, and fungicidal preparations. They have the formula Al₂(OH)_xCl_{3-x}, where *x* = 1–5, and are prepared by the reaction of an excess of aluminum with 5–15° hydrochloric acid at a temperature of 67–97°C (18). The same compounds are obtained by hydrolyzing aluminum alkoxides with hydrochloric acid (19,20) (see ALKOXIDES, METAL). Basic aluminum chloride has also been prepared by the reaction of an equivalent or less of hydrochloric acid with aluminum hydroxide at 117–980 kPa (17–143 psi) (20).

Aluminum chloride solutions used in antiperspirants and deoderant preparations must be buffered for the protection of skin and clothing (see COSMETICS). Lactic acid [598-82-3] is usually employed for neutralizing these formulations. Hydrates of aluminum chloride and basic aluminum chlorides are also effective in a number of difficult water treatment problems (see FLOCCULATING AGENTS). A polymeric form, called polyaluminum chloride, is added in amounts of 50–500 ppm and the pH adjusted to about 6.5 in the presence of treatment aids such as emulsion breakers, anionic surfactants, diatomaceous earth, or a high molecular weight flocculant. The resulting floc may be separated by aeration and flotation, settling and decantation, electrophoresis, or filtration. Latex, acrylic paint and oil emulsions, dyes, clay suspensions, and effluent from sanitary waste digestion respond to this treatment (see ALUMINUM COMPOUNDS, POLYALUMINUMS).

ALUMINUM BROMIDE

Anhydrous aluminum bromide, AlBr₃, forms colorless trigonal crystals and exists in dimeric form, Al₂Br₆, in the crystal and liquid phases (1). Dissociation of the dimer to the monomer occurs in the gas phase. The bromide is produced commercially only in small quantities. This product melts at 97.45 °C, boils at 256°C, and has a specific gravity at 25°C of 3.01.

Aluminum halides change from ionic to covalent character as the electronegativity of the halogen decreases (F > Cl > Br > I). Aluminum bromide, because of its covalent nature, is more soluble in many organic solvents than anhydrous aluminum chloride. Although its catalytic activity is moderate, it can be used in Friedel-Crafts reactions (qv) where selectivity is important (12). Anhydrous aluminum bromide, prepared from bromine [7726-95-6] and metallic aluminum, decomposes upon heating in air to bromine and alumina. Caution should be exercised in handling this hazardous compound because of its reactivity with water. Aluminum bromide may cause tissue burns, and both the anhydrous and the hydrate forms may be toxic upon ingestion.

Aluminum bromide hexahydrate [7784-11-4], AlBr₃·6H₂O, may be made by dissolving aluminum or aluminum hydroxide in hydrobromic acid [10035-10-6], HBr. This white, crystalline solid is precipitated from aqueous solution.

ALUMINUM IODIDE

Aluminum iodide [7884-23-8], AlI₃, is a crystalline solid with a melting point of 191°C. The presence of free iodine in the anhydrous form causes the platelets to be yellow or brown. The specific gravity of this solid is 3.98 at 25°C. Aluminum iodide hexahydrate [10090-53-6], AlI₃·6H₂O, and aluminum iodide pentadecahydrate [65016-30-0], AlI₃·15H₂O, are precipitated from aqueous solution. They may be prepared by the reaction of hydroiodic acid [10034-85-2], HI, with aluminum or aluminum hydroxide.

ALUMINUM NITRATE

Aluminum nitrate is available commercially as aluminum nitrate nonahydrate [7784-27-2], Al(NO₃)₃·9H₂O. It is a white, crystalline material with a melting point of 73.5°C that is soluble in cold water, alcohols, and acetone. Decomposition to nitric acid [7699-37-2], HNO₃, and basic aluminum nitrates [13473-90-0], Al(OH)_x(NO₃)_y, where *x* + *y* = 3, begins at 130°C, and dissociation to aluminum oxide and oxides of nitrogen occurs above 500°C.

Aluminum nitrate nonahydrate is prepared by dissolving aluminum or aluminum hydroxide in dilute nitric acid, and crystallizing the product from the resulting aqueous solution. It is made commercially from aluminous materials such as bauxite. Iron compounds may be extracted from the solution with naphthenic acids (21) before hydrate precipitation. In the laboratory it is prepared from aluminum sulfate and barium nitrate.

Anhydrous aluminum nitrate [13473-90-0] is covalent in character, easily volatilized, and decomposes on heating (22). Hydrated aluminum nitrate is used in the preparation of insulating papers, on transformer core laminates, and in cathode-ray tube heating elements. Solution of aluminum hydroxide through digestion of core materials in nitric acid has been proposed in aluminum extractive metallurgy. The resulting solution of aluminum nitrate is separated from other metal ions, and the aluminum oxide is recovered by thermal decomposition of the aluminum nitrate solution (23,24).

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ALUMINUM OXIDE (ALUMINA)

Activated,
Calcined, Tabular, and Aluminate Cements,
Hydrated,

ACTIVATED

The activated aluminas comprise a series of nonequilibrium forms of partially hydroxylated aluminum oxide [1344-28-1], Al_2O_3 . The chemical composition can be represented by $\text{Al}_2\text{O}_{3-x}(\text{OH})_{2x}$ where x ranges from about 0 to 0.8. They are porous solids made by thermal treatment of aluminum hydroxide [21645-57-2] precursors and find application mainly as adsorbents, catalysts, and catalyst supports. Activated alumina, for purposes of this discussion, refers to thermal decomposition products (excluding α -alumina [12252-63-0]) of aluminum trihydroxides, oxide hydroxides, and nonstoichiometric gelatinous hydroxides. The term "activation" is used in this article to indicate a change in properties resulting from heating (calcining). Other names for these products are active alumina, gamma alumina, catalytic alumina, and transition alumina. Transition alumina is probably the most accurate because the various phases identified by x-ray diffraction are really stages in a continuous transition between the disordered structures immediately following decomposition of the hydrous precursors and the stable α -alumina which is the product of high temperature calcination.

Physical and Chemical Properties

In general, as a hydrous alumina precursor is heated, hydroxyl groups are driven off leaving a porous solid structure of activated alumina. The transformation is topotactic and little change in size or shape of the material is observed at low magnifications. At magnifications higher than about 10,000, changes in texture resulting from recrystallization can be seen. The physical properties of the material are set by the choice of precursor, the forming process, and the activation conditions.

Figure 1 shows the decomposition sequence for several hydrous precursors and indicates approximate temperatures at which the activated forms occur (1). As activation temperature is increased, the crystal structures become more ordered as can be seen by the x-ray diffraction patterns of Figure 2 (2). The similarity of these patterns combined with subtle effects of precursor crystal size, trace impurities, and details of sample preparation have led to some confusion in the literature (3). The crystal structures of the activated aluminas have, however, been well-documented by x-ray diffraction (4) and by nmr techniques (5).

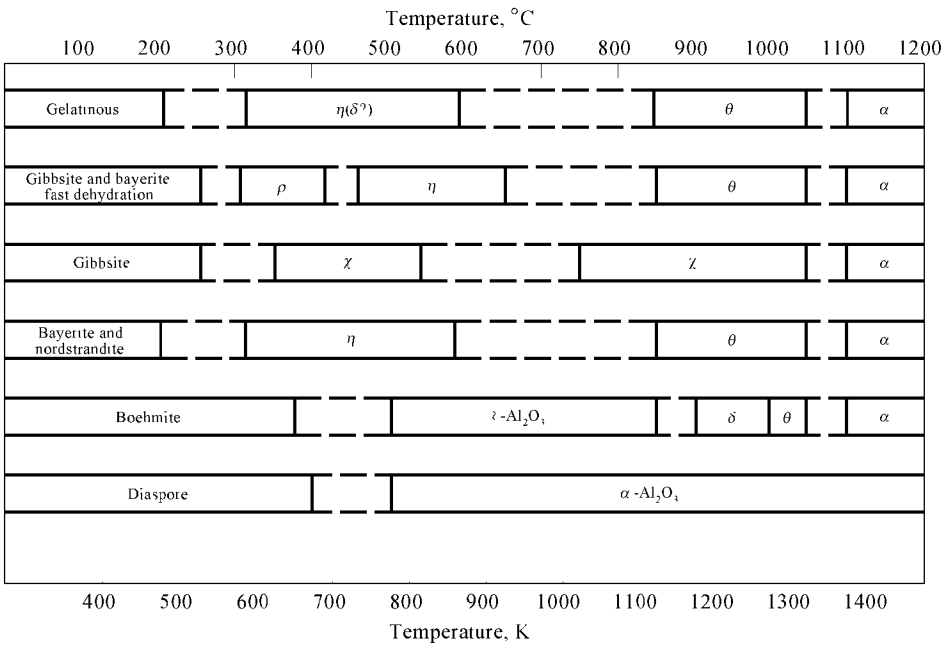


Fig. 1. Decomposition sequence of hydrous aluminas.

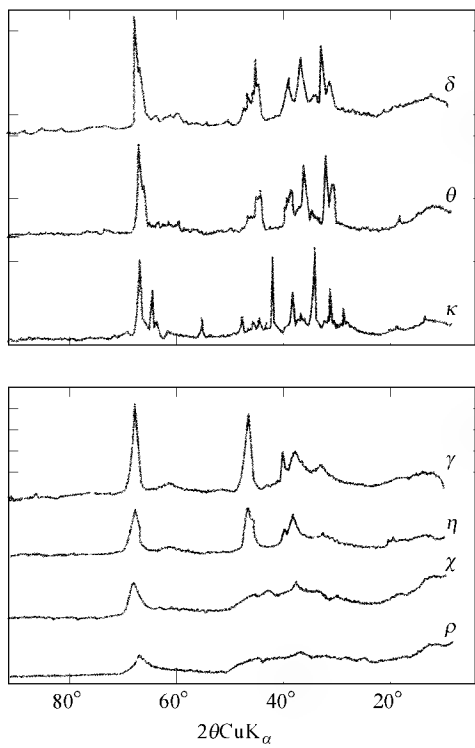


Fig. 2. X-ray diffraction patterns of transition aluminas.

Decomposition of Boehmite. Boehmite [1318-23-6], $\text{AlO}(\text{OH})$, can be synthesized having surface areas ranging from about 1 to over 800 m^2/g depending upon the method of preparation (6). The properties of activated boehmite products are strongly influenced by the crystallite size of the precursor material (7). When a crystallized, low surface area boehmite is heated, conversion to gamma alumina occurs at about 725 K yielding a low surface area product having a well-defined x-ray pattern. On further heating, the transition follows the gamma-delta-theta-alpha sequence shown in Figure 1. In contrast, a very high surface area boehmite (also referred to as pseudoboehmite or gelatinous boehmite) decomposes at 575–625 K yielding a high surface area product having a poorly defined gamma alumina x-ray pattern. On further heating, the transformation of this material to delta and theta phases may be retarded or may not occur at all, depending upon trace impurities (8). This sequence is also indicated in Figure 1. Figure 3 shows surface areas of three boehmite samples having different initial surface areas after heating for 16 hours at various temperatures. In the low temperature region, the highest surface area starting material maintains a higher surface area than the others, but in the range where delta-theta phases would be expected, the curves converge. This loss of surface area is a manifestation of coarsening of the activated alumina crystals and is also accompanied by a shift toward larger pore sizes on heating (9). In the high surface area materials, the surface area is mostly attributable to the external surface area of the precursor crystallites. Evolution of internal pore structure has been well-documented for activation of well-crystallized boehmite (10), but this is only a minor contribution to surface areas of the commercially important activated boehmites, typically in the 200–350 m^2/g range (11,12). Loss of surface area on heating is inevitable, but can be either retarded or accelerated by various additives (13).

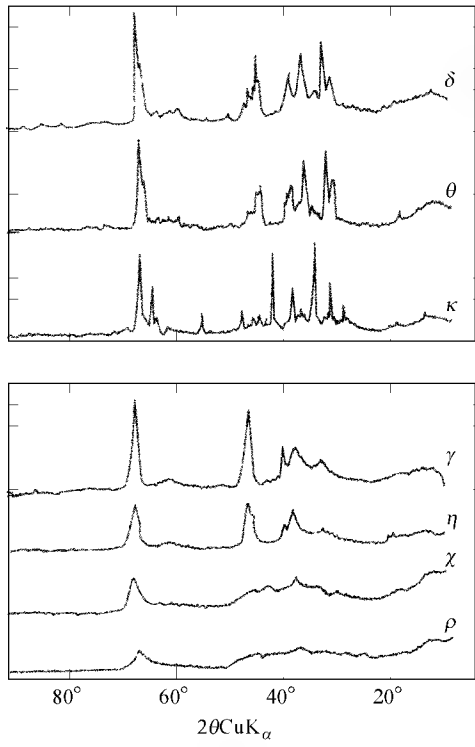


Fig. 3. Surface area of boehmite samples after activation, where A and B are experimental boehmite and C is Catapal SB.

Activation Products of Aluminum Hydroxide. Figure 4 shows the effect of temperature on some properties of activated alumina produced by heating gibbsite [14762-49-3], $\alpha\text{-Al}(\text{OH})_3$ (14). As the material is heated, surface area reaches a maximum of 300 m^2/g or more at about 650 K. As temperature is increased further, surface area decreases and the skeletal structure becomes more dense reflecting increased ordering of the crystalline structure during the progression from chi to kappa to alpha. At about 1450 K conversion to alpha alumina occurs with a major rearrangement of crystal structure and corresponding decrease in surface area to about 5 m^2/g . These trend vary somewhat according to precursor crystal size, purity, and the atmosphere of heating.

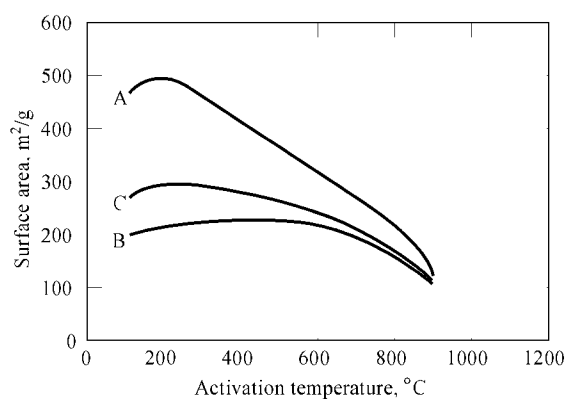


Fig. 4. Properties of activated gibbsite, where ρ represents density, Δ is the loss of ignition, and — is specific surface area.

Unlike the case for boehmite, the surface area of activated gibbsite results mainly from internal porosity rather than external surface of the precursor. There is a minor effect of initial crystal size, however. Some (10% or less) boehmite tends to form when coarse crystals of gibbsite are activated because of hydrothermal conditions which are generated in the particles. On further activation, this boehmite decomposes, but contributes little to the overall surface area. For this reason, activation of fine gibbsite tends to give somewhat higher maximum surface areas than coarser material (15). High humidity in the activating gas can also promote boehmite formation and lower surface area.

Activation of bayerite [20257-20-9] and nordstrandite [13840-05-6] qualitatively follows the pattern shown in Figure 4, but the transition sequence is eta-theta-alpha. The structures of these transition phases are somewhat different from those obtained from gibbsite, reflecting the differences in crystal structure of the hydroxides (16).

If aluminum hydroxide is decomposed by heating at low temperature under vacuum or by rapidly heating at high temperature, a nearly amorphous (x-ray indifferent) phase known as rho alumina is produced which has the interesting property of recrystallizing (rehydrating) to boehmite or bayerite when mixed with water (17). This behavior is known as rehydration bonding and occurs to a significant degree in hot water at atmospheric pressure (18). Rho alumina can be formed from any of the aluminum hydroxides. The crystal structures are probably somewhat different depending upon which precursor (gibbsite or bayerite) is used, but this cannot be detected by x-ray and rehydration properties are similar. Some recrystallization to boehmite occurs in all of the activated aluminas under severe hydrothermal conditions and generally the degree to which this occurs decreases with increased crystalline order (higher activation temperature). The ease with which rho alumina rehydrates sets it apart from the other activated alumina phases.

Except for rho alumina, the activated aluminas are quite stable when mixed with water in the pH range from about 4 to 10. Below pH 2 and above pH 12 they degrade rapidly.

The surface of activated alumina is a complex mixture of aluminum, oxygen, and hydroxyl ions which combine in specific ways to produce both acid and base sites. These sites are the cause of surface activity and so are important in adsorption, chromatographic, and catalytic applications. Models have been developed to help explain the evolution of these sites on activation (19). Other ions present on the surface can alter the surface chemistry and this approach is commonly used to manipulate properties for various applications.

Manufacturing Processes

The large majority of activated alumina products are derived from activation of aluminum hydroxide, rehydrated alumina, or pseudoboehmite gel. Other commercial methods to produce specialty activated aluminas are roasting of aluminum chloride [7446-70-0], AlCl_3 , and calcination of precursors such as ammonium alum [7784-25-0], $\text{Al}(\text{NH}_4)_2(\text{NO}_3)_2$. Processing is tailored to optimize one or more of the product properties such as surface area, purity, pore size distribution, particle size, shape, or strength.

Activated Aluminum Hydroxide. The principal precursor for this class of products is gibbsite derived from the Bayer process although a small amount of bayerite is also used for some specialty catalytic applications. Bayer process gibbsite is available in very large tonnages as an intermediate product in aluminum production. It is 99+% pure; the main impurity is sodium oxide [1313-59-3], Na_2O , at 0.2–0.3% on a $\text{Al}(\text{OH})_3$ basis. Low cost, relatively high purity, and availability make gibbsite the raw material of choice for many activated alumina products.

Gibbsite is a free-flowing powder having a median particle diameter of about 100 micrometers. Traditionally, activated alumina powders were produced by passing this material through a rotary kiln at an appropriate temperature. However, the aluminum industry has developed fluid bed and flash heating technology for calcination of metallurgical alumina and Bayer alumina-based activated aluminas are often produced in this type of equipment (20,21). The particle sizes of the activated aluminas are essentially the same as that of the precursor powder and in the unground form are amenable to applications involving fluid bed handling. These powders can also be ground to sizes of 10 micrometers or less by standard techniques. Conventional activated aluminas are produced by slow heat treatment whereas "rehydratable" powders are activated within a few seconds.

Larger particle size products can be produced by direct activation of agglomerated gibbsite. The oldest product of this class is made from "scale" which forms on the walls of Bayer process precipitators and is periodically removed in massive chunks, then crushed and activated. This gives a granular product, having particle sizes up to 1 cm or more, which has good mechanical properties and is relatively inexpensive. A similar product is manufactured by high pressure compaction of gibbsite powder. Once the gibbsite agglomerates are formed they are converted to the desired activated alumina product by a combination of crushing, screening, and heat treatment.

Unrefined bauxite [1318-16-7] is also used as a precursor to low cost activated alumina because bauxites can contain as much as 90% gibbsite (dry basis). These materials represent the low cost, low performance end of the activated alumina spectrum of products, but they are still used in significant quantities.

Rehydration Bonded Alumina. Rehydration bonded aluminas are agglomerates of activated alumina, which derive their strength from the rehydration bonding mechanism. Because more processing steps are involved in the manufacture, they are generally more expensive than activated aluminum hydroxides. On the other hand, rehydration bonded aluminas can be produced in a wider range of particle shape, surface area, and pore size distribution.

The generic process used to manufacture these materials begins with an activated powder produced by rapid (flash) activation and grinding of Bayer process gibbsite. This powder is generally composed of a mixture of chi and rho forms, the proportion depending upon the specifics of the activation process. The powder is then mixed with water and formed into a shape by tumbling (22), extrusion (23), or dropping a slurry into an immiscible fluid (oil-drop) (24,25). During or after the forming process, the shapes are heated without drying from several minutes to several hours at temperatures between about 330 and 370 K. This allows partial rehydration to occur, rigidizing the structure. At this point, the alumina is a mixture of pseudoboehmite, bayerite, chi, and amorphous phases (18,22). The shapes are then given a second heat treatment or calcination to establish the desired degree of activation. The surface area, which depends upon the micropores, is largely determined by the second heat treatment whereas the total pore volume is set by specifics of the forming operation. Activated aluminas prepared by this method are mixtures of phases reflecting the composition after rehydration.

Gel-Based Activated Aluminas. Alumina gels can be formed by wet chemical reaction of soluble aluminum compounds. An example is rapid mixing of aluminum sulfate [17927-65-0], $\text{Al}_2(\text{SO}_4)_3 \cdot \text{XH}_2\text{O}$, and sodium aluminate [1302-42-7], NaAlO_2 , solutions to form pseudoboehmite and a

near neutral sodium sulfate [7757-82-6] solution (26). After extensive washing to remove the sodium sulfate, the resulting gel can be dried or partially dewatered and formed directly by extrusion or oil drop. If the gel is dried prior to forming, it can be ground to fine particle size, then mixed with water and tumbled or formed by the general processes described above (27). The shapes are then activated to produce relatively pure phase gamma alumina. Gels made from aluminates and aluminum salts must be carefully washed to remove undesirable anions and cations which would be detrimental to the final application.

Hydrolysis of aluminum alkoxides is also used commercially to produce precursor gels. This approach avoids the introduction of undesirable anions or cations so that the need for extensive washing is reduced. Although gels having surface area over 800 m²/g can be produced by this approach, the commercial products are mostly pseudoboehmite powders in the 200–300 m²/g range (28). The forming processes already described are used to convert these powders into activated alumina shapes.

"Oil-drop" covers an interesting group of processes to produce small activated alumina spheres or beads by dispersing an aqueous alumina sol or solution in an immiscible liquid. The surface tension effects cause the aqueous droplets to attain a spherical shape and, while in this condition, they gel. Gellation can be accomplished by neutralization with ammonia (26,28), dehydration with alcohol, or through rehydration bonding (24). Beads of very uniform size have been generated by forming droplets of aluminum nitrate [13473-90-0], Al(NO₃)₃, solution using a specially designed nozzle, allowing them to be partially gelled with ammonia [7664-41-7] vapor then falling into an oil–ammonia solution for final gellation (29).

The gel-based products have traditionally been the most expensive and highest performance activated alumina products. They have very good mechanical properties, high surface area, and their purity and gamma-alumina structure make them somewhat resistant to thermal degradation. On the other hand, they are the most difficult to manufacture; and disposal of by-product salts can present an environmental problem.

Economic Aspects

In 1990 U.S. production of activated alumina was about 50,000 t/yr and bulk prices were mostly between \$0.60 and \$3.00/kg. The least expensive products are those derived directly from Bayer-process gibbsite and powders are generally less expensive than formed products. The soda content (0.2–0.3% Na₂O) of Bayer gibbsite makes it unattractive for many catalytic applications. Gel-based products are normally used where low soda level is required. Soda content of gels prepared from inorganic salts or aluminate solutions is typically about 0.03% whereas soda in alkoxide-based gels is much lower. Specialty activated aluminas having purity as high as 99.99% are also available at a much higher price.

Shaped products used for adsorbent purposes are generally less sophisticated and therefore less expensive than catalytic products. In 1985, it was reported that 10,000 t/yr of activated alumina adsorbents were produced in the United States. North American producers of Bayer process-based activated aluminas include Alcoa, La Roche (formerly Kaiser Chemicals), Discovery, and Alcan. Gel-based activated aluminas are produced by La Roche, Vista, and several of the major catalyst manufacturers. In Europe, principal sources of supply are Rh ne-Poulenc and Condea.

Safety and Handling

Activated alumina is a relatively innocuous material from a health and safety standpoint. It is nonflammable and nontoxic. Fine dusts can cause eye irritation and there is some record of lung damage because of inhalation of activated alumina dust mixed with silica [7631-86-9] and iron oxide [1317-61-9] (30). Normal precautions associated with handling of nuisance dusts should be taken. Activated alumina is normally shipped in moisture-proof containers (bags, drums, sling bins) because of its strong desiccating action.

Uses

Catalytic Applications. Activated alumina is used commercially in catalytic processes as a catalyst, catalyst substrate, or as a modifying additive. Activated alumina serves as the catalyst in the Claus process for recovering sulfur from H₂S that originates from natural gas processing or petroleum refinery operations (31). The alumina is generally in the form of spheres, about 5 mm in diameter. This size has evolved as a good compromise between high activity and low pressure drop for fixed bed application (32). Promoting the alumina using a small amount of alkali has been claimed to enhance performance in certain Claus operations (33) (see SULFUR REMOVAL AND RECOVERY).

The largest application for activated alumina as a catalyst substrate is in hydrotreating of petroleum feedstocks (qv) (34). The purpose of hydrotreating is threefold: to increase the H/C ratio; to remove O, S, and N impurities; and to remove V, Ni, and other tramp contaminants, especially from residuum of heavier feedstocks. Specialized alumina-based catalysts typically promoted with compounds of Co, Mo, W, and Ni have been developed for these operations (34). The catalysts are usually in the form of extrudates having variously shaped cross sections (35) (circular, lobed, wagon-wheel) about one millimeter in diameter. Spherical catalysts 1 mm or less in diameter have also been described for hydrotreating (24). Much attention has been given to optimizing pore volume and pore size distribution of the activated alumina substrates used in these operations and the "optimum" properties vary with operating conditions and the petroleum feedstock being processed. In the 1990s, worldwide consumption of hydrotreating catalysts was estimated at 30,000–40,000 t/yr, increasing at about 6%/yr (36,37).

Another catalytic application for promoted alumina is in automotive exhaust catalysts which enhance oxidation of hydrocarbons, carbon monoxide, and nitrogen oxide in exhaust gas (see EXHAUST CONTROL, AUTOMOTIVE). There are two general configurations of catalyst currently in use: beads and monoliths. In both systems, the catalytic component is precious metal (platinum, palladium, and rhodium) on alumina (38). The bead system consists of a bed of 3-mm diameter alumina spheres which act as both catalyst substrate and mechanical support. In the monolith system, the mechanical support is provided by a porous ceramic (cordierite [12182-53-5]) multichannel "honeycomb" having a thin alumina coating (washcoat) as the catalytic substrate. Automotive exhaust catalyst was the largest volume application (about 18,000 t/yr) for promoted alumina in the mid-1970s and was a significant driving force in improving the technology of low density alumina sphere manufacture. Since that time, however, monoliths have become the system of choice for this application. Beads have maintained only a small share of the market and consequently the volume of activated alumina used in automotive catalysts has dropped significantly (39).

The largest tonnage single application for catalyst particles is in fluid cracking (FCC). 1990 U.S. consumption is projected to be about 180,000 tons (40). These materials are typically made from zeolite having a clay or alumina–silica binder system to provide the necessary mechanical strength for fluid bed handling. Addition of alumina (aluminum hydroxide, pseudoboehmite, or rehydratable alumina) to these formulations has been reported to improve various properties (41,42). Any alumina powder would be activated under FCC processing conditions, thus the activated alumina is used as a modifying additive in the catalytic process. The actual usage of activated alumina in FCC catalysts is unclear because of the highly competitive and proprietary nature of this market.

A number of smaller but nevertheless important applications in which activated alumina is used as the catalyst substrate include: alcohol dehydration, olefin isomerization, hydrogenation, oxidation, and polymerization (43).

Chromatographic Applications. Activated alumina has been used for many years in the separation of various organic compounds by normal phase chromatography (qv) because of its natural hydrophilic surface characteristics. More recently, stable surface coatings have been developed which impart hydrophobic properties to the particle surface (44). These coatings, coupled with improved technology to produce closely sized particles have allowed alumina to compete in reverse-phase chromatographic markets. Compared to silica, the dominant reverse-phase packing material, alumina has better chemical stability at moderately high pH levels, which gives it a natural advantage for separations in this pH range (45).

Membranes. Membranes comprised of activated alumina films less than 20 µm thick have been reported (46). These films are initially deposited via sol–gel technology (qv) from pseudoboehmite sols and are subsequently calcined to produce controlled pore sizes in the 2 to 10-nm range. Inorganic membrane systems based on this type of film and supported on solid porous substrates have been introduced commercially. They are said to have better mechanical and thermal stability than organic membranes (47). The activated alumina film comprises only a miniscule part of the total system (see MEMBRANE TECHNOLOGY).

Adsorbent Applications. One of the earliest uses for activated alumina was removal of water vapor from gases and this remains an

important application. Under equilibrium conditions alumina adsorbs an increasing amount of water as the relative humidity of the contacting gas increases. At 50° o rh, for example, a good quality activated alumina can adsorb water at levels of 15 to 20° o or more of its own weight (48). By heating the activated alumina to about 525 K under low rh conditions, essentially all of the adsorbed water is removed and the alumina is returned to its original state. This adsorption–regeneration cycle can be repeated hundreds of times with little deterioration of the adsorbent. Industrial scale countercurrent drying systems use this cyclic approach, but generally are designed for lower water loadings because economic cycle times are too short for equilibrium to be established. Another consideration in the large beds of industrial dryers is the amount of heat generated which amounts to about 46 kJ mol (11 kcal mol) of water adsorbed. A common strategy is to operate the drying systems under pressure. This partially reduces the water content in the gas before it enters the bed by condensation and also increases the heat capacity of the gas, facilitating heat removal from the bed (49). Under proper operating conditions, moisture in the dried gas can be as low as 11 ppmv. The usual forms of activated alumina used in desiccant applications are granules or spheres about 3 to 12 mm in size. Besides air, a partial list of gases that can be dried includes Ar, He, H₂, CH₄, C₂H₂, C₃H₈, C₂H₂, C₂H₄, C₃H₄, Cl₂, HCl, SO₂, NH₃, and fluorochloroalkanes. Activated alumina is also used to remove water from organic liquids including gasoline, kerosene, oils, aromatic hydrocarbons, cyclohexane, butane and heavier alkanes, butylenes, and many chlorinated hydrocarbons.

Besides drying applications, activated alumina is used to selectively remove various species from gas and liquid systems. In refining and petrochemical operations, activated alumina is used to remove trace HCl from reformer hydrogen, fluorides from hydrocarbons produced by HF alkylation, and a variety of other stream cleanup applications (48). An important example in air pollution abatement is adsorption of fluoride vapors emanating from the aluminum smelting operation (see ALUMINUM AND ALUMINUM ALLOYS). Fluoride-contaminated air from the smelting cell area is countercurrently passed through fluid beds of alumina cell feed which adsorbs the fluorides for recycle. Fluorides are also effectively removed from potable water by activated alumina (50). Fluoride tends to adsorb on alumina at low pH levels and desorb (regenerate) when the pH is increased so in these systems, regeneration of the alumina adsorbent is accomplished by pH control rather than thermal treatment. Arsenic has also been effectively removed from potable water by activated alumina (51). Activated alumina is receiving renewed attention as an adsorbent and a wealth of information has been published on adsorption characteristics of many chemical species (52,53).

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CALCINED, TABULAR, AND ALUMINATE CEMENTS

CALCINED ALUMINA

Calcined aluminas are generally obtained from Bayer process gibbsite [14762-49-3], α -Al(OH)₃ (1-8), thermal decomposition of which follows the transition through the generic gamma alumina phases to α -alumina [1302-74-5] (corundum), α -Al₂O₃. Nonmineralized metal-grade or smelter-grade alumina (SGA) for aluminum production is calcined at lower temperatures and usually contains about 20 to 50% α -Al₂O₃. The remainder consists of higher temperature transition aluminas, usually theta, kappa, delta, and gamma, depending upon the consolidation of the original gibbsite structure, impurities, heating rate, and furnace atmosphere. Figure 1 (9) shows the changes in gibbsite upon heating for one hour where no mineralizers are added. Loss on ignition (LOI), total water, and surface area may be used to define the degree of calcination of Bayer hydrates.

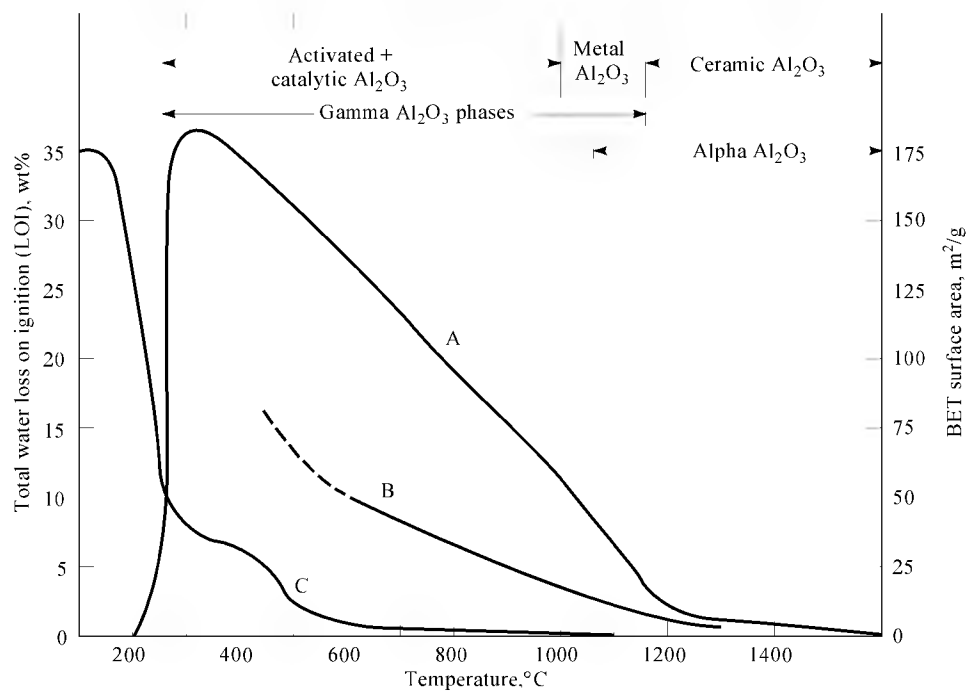


Fig. 1. Normal soda Bayer hydrate heated for one hour. A, change in surface area; B, total water, LOI plus sorbed water after exposure to 44% rh; and C, water loss on ignition when heated to 1100°C.

Nonmineralized SGA flows freely, and is often known as sandy alumina because it easily covers the cryolite bath of aluminum electrolysis cells (see ALUMINUM COMPOUNDS, INTRODUCTION). Properties typical of a sandy SGA are shown in Table 1. Aluminum smelting technology in the United States is primarily based upon sandy alumina. Older European smelting technology, however, is based upon a poor flowing, low bulk density, highly mineralized SGA called floury alumina, composed principally of α -Al₂O₃.

Table 1. Properties of Sandy SGA Metallurgical Alumina^a

Property	Value
α -Al ₂ O content, wt % ^b	20
specific surface area, m ² /g	50–80
particle size distribution, wt %	
+100 mesh ^c	5
+325 ^d	92
325 ^e	8
bulk density, kg/L	
loose	0.95–1.00
packed	1.05–1.10
attrition index, wt % ^f	4–15
moisture at 573 K, wt %	1.0
loss on ignition, 573 to 1473 K, wt %	1.0
chemical composition, wt %	
Fe ₂ O ₃	0.020
SiO ₂	0.020
TiO ₂	0.004
CaO	0.040
Na ₂ O	0.500

^a Ref. 6.

^b Determined by optical or x-ray method.
^c Retained on 100 mesh 149 μm Tyler screen.
^d Retained on 325 mesh 44 μm Tyler screen.
^e Passes through 325 mesh 44 μm Tyler screen.
^f A 44 μm increase is observed by the modified Forsythe- Hertwig fluidizing test method.

Specialty alumina derived from the Bayer process resemble SGA, except for a higher α-Al₂O₃ content, which is usually >80%, and a lower surface area, typically <20 m² g. The remaining material is generally sodium β-alumina (Table 2) formed as a result of the soda contamination common to the process (2–7). The mineralogical and structural properties of calcined aluminas are given in Table 2 (3).

Table 2. Structural Properties of Transition Aluminas^a

Phase	CASRegistry Number	Formula	Crystalsystem	Spac egro up	Molecules perunit cell	Unit cell length, nm			Density, g cm ³
						a	b	c	
gamma		γ-Al ₂ O ₃	tetragonal			0.562	0.780		3.2 ^b
delta		δ-Al ₂ O ₃	orthorhombic		12	0.425	1.275	1.021	3.2 ^b
theta ^c kappa		θ-Al ₂ O ₃ κ-Al ₂ O ₃	tetragonal monoclinic	C ³ _{2h}	4	0.796		2.34	3.56
			hexagonal			1.124	0.572	1.174	
α-alumina (corundum)	[1302-74-5]	α-Al ₂ O ₃	hexagonal	D ³ _{2d}	2	0.971		1.786	3.1–3.3
			hexagonal			0.970		1.786	
			hexagonal			1.678		1.786	
			hexagonal (rhombic)			0.475		1.299	
sodium β-aluminate	[1302-42-7]	NaAlO ₂	orthorhombic	C ⁹ _{2v}	4	0.537	0.521	0.707	2.693
sodium β-alumina	[11138-49-1]	Na ₂ O · 11Al ₂ O ₃	tetragonal	D ⁴ _h	1	0.532		0.705	3.24
sodium β-alumina	[12005-48-0]	Na ₂ O · 5Al ₂ O ₃	hexagonal			0.558		2.245	
potassium β-alumina	[12005-47-9]	K ₂ O · 11Al ₂ O ₃	hexagonal	D ⁴ _h	1	0.561		3.395	3.30
magnesium β-alumina	[12428-93-2]	MgO · 11Al ₂ O ₃	hexagonal	D ⁴ _h	1	0.558		2.267	
calcium β-alumina	[12005-50-4]	CaO · 6Al ₂ O ₃	hexagonal	D ⁴ _h	2	0.556		2.255	3.69
strontium β-alumina	[12254-24-9]	SrO · 6Al ₂ O ₃	hexagonal	D ⁴ _h	2	0.554		2.183	
barium β-alumina	[12254-17-0]	BaO · 6Al ₂ O ₃	hexagonal	D ⁴ _h	2	0.556		2.195	3.69
lithium δ-alumina	[12005-14-0]	Li ₂ O · 5Al ₂ O ₃	hexagonal	D ⁴ _h	2	0.558		2.267	
			cubic	O ⁷ _h	2	0.790			3.61

^a Ref. 3.
^b Estimated.
^c Unit cell angle is 103°20′.

α-Alumina, the stable form of anhydrous alumina, occurs in nature as corundum, some varieties of which are natural abrasives (qv). It is common to igneous and metamorphic rocks and the red and blue varieties of gem quality are called ruby [12174-49-1] and sapphire [1317-82-4], respectively (6). The corundum structure consists of alternating layers of Al and O (10).

Commercial Bayer calcined aluminas, other than for aluminum production, contain substantial amounts of α-Al₂O₃. α-Al₂O₃ also results industrially from solidification of molten alumina to form artificial sapphires, abrasives, or other corundum varieties (see GEMS, SYNTHETIC) or else by sintering processes (tabular aluminas). Properties include extreme hardness, resistance to wear and abrasion, chemical inertness, outstanding electrical and electronic properties, good thermal shock resistance and dimensional stability, and high mechanical strength at elevated temperatures (see ADVANCED CERAMICS; CERAMICS; GLASS; ENAMELS).

Shapes fabricated from ground, calcined α-Al₂O₃ powders have reached 98% theoretical density at temperatures below 1723 K even though α-Al₂O₃ melts at 2326 K. The fine (submicrometer) hexagonal crystals obtained during calcination permit sintering to occur at much lower temperatures after supergrinding to dislodge the individual crystals from the Bayer agglomerate. These thermally reactive, fine-crystalline, fully ground α-Al₂O₃ products have been classified as reactive aluminas by the alumina ceramic industry, because they densify at lower sintering temperatures. The increased reactivity corresponds to decreasing sintering temperatures achieved by decreasing crystal size.

Preparation

Calcination of gibbsite has been done in rotary kilns for many years. Specialty calcined aluminas can also be prepared in stationary or fluid bed calciners (see FLUIDIZATION) similar to those used for producing SGA. Fluid-flash calciners producing up to 1500 t/d provide a 30–40% fuel savings compared to the rotary kiln (11). Only a few specialty calcines have sufficient commercial requirements to justify manufacture in these high production capacity fluid-flash calciners. The resulting calcined products have degrees of crystallization that vary according to the temperature, the duration of the calcination, and whether or not mineralizers are used (1–4,7,9). Mineralizer usage reduces the temperature and enhances α-Al₂O₃ crystal growth. Data for a wide variety of calcined alumina is available (1,12,13).

Rotary kiln production is preferred for coarse crystalline products which are easily attrited. Particle breakdown causes dust and materials handling problems but electrostatic precipitators are used to remove particulates from combustion products (see POWDER HANDLING). The particle size of unground calcined Bayer alumina is primarily controlled during precipitation: very little particle shrinkage occurs during calcination, even though 3 moles of water of crystallization is lost. The resulting unground porous agglomerates are nominally 100 to 325 mesh (149 to 44 μm). Scanning electron microscope (sem) data differentiates between unground Bayer agglomerates (Fig. 2) which can have crystals as fine as 0.5 μm and as large as 15 μm. Physical properties begin to correlate with crystal size above about 2–3 μm. As crystal size increases, bulk density decreases, angle of repose increases, attrition rate increases, and thus, bulk handling characteristics worsen.

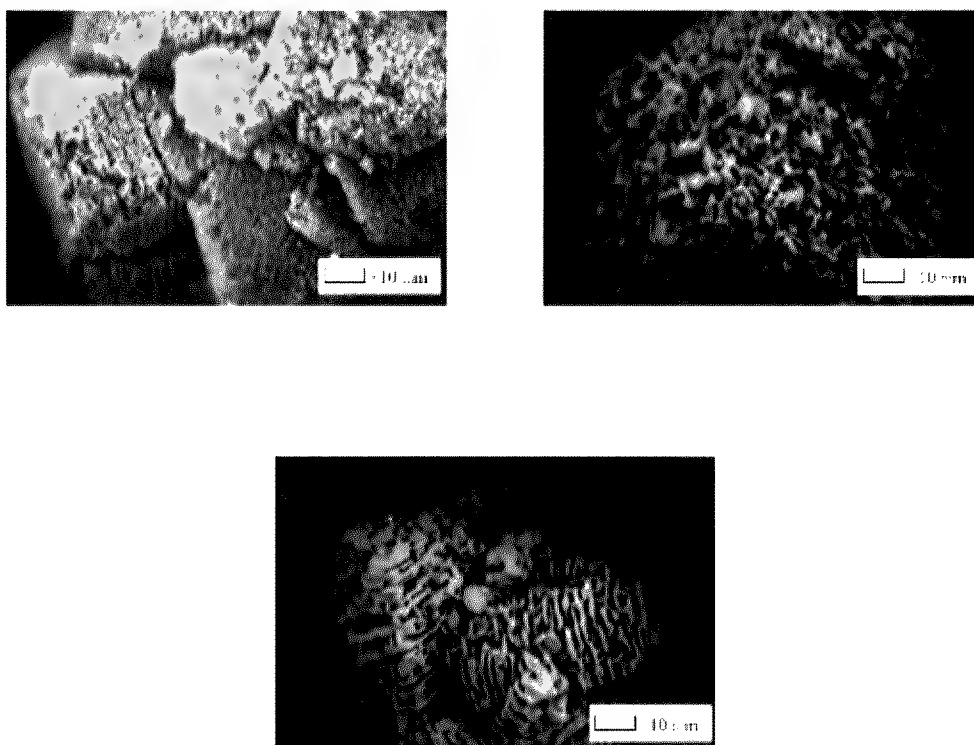


Fig. 2. Sem photographs of controlled crystal size aluminas.

Soft-burned calcined products having α - Al_2O_3 crystals no larger than $1\text{ }\mu\text{m}$ may include a considerable portion of transition aluminas (1–7) and exhibit specific surfaces as high as $50\text{ m}^2/\text{g}$. Most special calcined products are 80–100% α - Al_2O_3 and have a specific surface area from <0.5 to $>20\text{ m}^2/\text{g}$. A considerable portion of the normal 0.3–0.6% Na_2O contained in Bayer alumina is in the form of β -alumina, $\text{Na}_2\text{O} \cdot 11\text{Al}_2\text{O}_3$.

Special calcined alumina can be broadly categorized according to soda content in addition to crystal size. Besides the normal soda products, special grades are made at the intermediate (0.15–0.25% Na_2O) and low ($<0.1\%$ Na_2O) soda levels. Extra high purity 0.5 μm calcines, typically 99.95% Al_2O_3 having less than 0.01% Na_2O , are also available in ton quantities.

Ground, Calcined, and Reactive Aluminas. Most ceramic grade aluminas are supplied dry ground to about 95% 325 mesh (44 μm) using 85–90% Al_2O_3 ceramic ball, attrition, vibro-energy, or fluid-energy milling. Particles larger than 44 μm can be removed by air classification during continuous milling to produce 99+% 325 mesh product. More fully ground, or superground, calcined aluminas having particle size distributions that approximate the natural or ultimate crystal size of the Bayer grain as calcined are often desired (8).

Thermally reactive aluminas contain submicrometer crystals. These must be separated from the Bayer agglomerate during grinding to permit dense compaction upon ceramic forming, and thus, enhance densification upon sintering at lower temperatures (14–21). Usually from 10 to greater than 30 hours dry batch ball milling is required for this separation. Such superground, thermally reactive aluminas exhibit higher densification rates when compacted and sintered into ceramic products and complete densification is obtained about 200 °C lower than using the coarser, continuously ground aluminas (1).

Severe mill packing problems can occur in dry batch-milling aluminas and dry grinding aids may be used (14,15). These sorb on the surface of the aluminas, reduce the energy required to separate the individual crystals from the Bayer agglomerates and prevent mill packing by developing repelling surface charges on the alumina crystals. Mill packing tendencies also decrease with increasing mill size and ball-to charge ratio.

Reactive aluminas have enabled 85, 90, and 95% Al_2O_3 ceramics to be upgraded (16,17), because they could be sintered without fluxes in the temperature range of about 1723–2023 K, rather than 2073–2123 K. Advances in microminiaturization of components for the electronic, computer, and aerospace industries have been directly related to the development of low soda and reactive aluminas (18).

Specialty Aluminas. Process control (qv) techniques permit production of calcined specialty aluminas having controlled median particle sizes differentiated by about 0.5 μm . This broad selection enables closer shrinkage control of high tech ceramic parts. Production of pure 99.99% Al_2O_3 powder from alkoxide precursors (see ALKOXIDES, METAL), apparently in spherical form, offers the potential of satisfying the most advanced applications for calcined aluminas requiring tolerances of $\pm 0.1\%$ shrinkage.

The difficulty of dispersing superground aluminas which contain dense, repelletized agglomerates is illustrated in Figure 3a. Deflocculated 0.5 μm material is only partially dispersed when magnetically stirred, in comparison to the completely dispersed sample produced by using an ultrasonic probe. In contrast, the dispersible alumina is essentially fully dispersed as shown in Figure 3b (8). This product, with agglomerates mechanically disintegrated, also disperses fully in 3 to 5 min where low shear mixers used to homogenize refractories are employed. Improved predictability of the rheology and forming characteristics of advanced refractory mixes results.

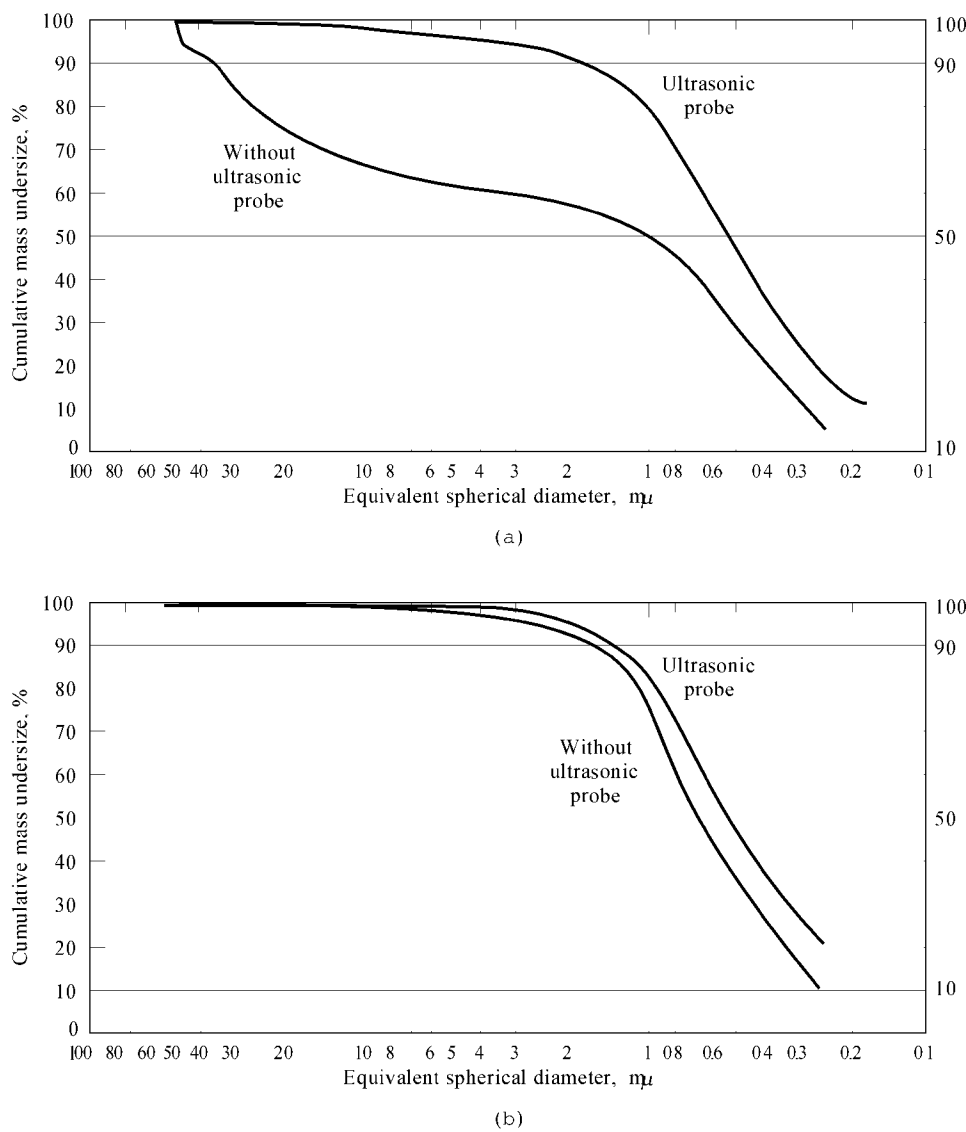


Fig. 3. Sedigraph particle size distribution for superground submicrometer alumina. (a) Partially dispersed; (b) fully dispersed.

Uses

Calcined alumina markets consume slightly less than 50% of the specialty alumina chemicals production (1–8,20,22–115). Worldwide usage is estimated to be about 50% for refractories (qv), 20% for abrasives, and 25% for ceramics (qv). Calcined aluminas are also used in the manufacture of tabular alumina and calcium aluminate cements (CAC). Quantities are estimated to be over 200,000 and 100,000 t, respectively (7).

Ceramics. Calcined aluminas are used in both electronic and structural ceramics (see *ADVANCED CERAMICS*). Electronic applications are dominant in the United States and Japan whereas mechanical applications are predominant in Europe (1). Specialty electronic integrated circuit packages generally use the low soda and thermally reactive aluminas.

Enamels, glass, chinaware glazes, china and hotel ware, and electrical porcelain insulators usually contain 5 to 25% alumina additions to increase strength and chip resistance, whereas electronic and mechanical alumina ceramics contain greater than 85% Al_2O_3 as calcined alumina. Coarse crystalline (2 to 10 μm) aluminas having 0.05 to 0.20% Na_2O are used in spark plug insulators which is the largest use of alumina in the electronics field. High purity 99.99% Al_2O_3 (2,3) is used to make translucent polycrystalline alumina tubes for sodium vapor lamps. Traditional glass tubes allow significant sodium diffusion at the operating temperatures of the sodium vapor lamps. All varieties of calcined aluminas are used in mechanical and technical applications. But when optimum hardness, density, and wear resistance are required, the thermally reactive aluminas are used in 95% and higher Al_2O_3 compositions. Lower price, normal soda calcined aluminas are used in compositions as low as 85% Al_2O_3 whenever lower performance can be tolerated.

Cutting tools of thermally reactive, high purity aluminas in combination with zirconia, titanium carbide or titanium nitride, the SIALONS, and boron, nitride have high mechanical strength, fracture toughness, and cutting behavior for high speed cutting of hard steel and cast iron. High mechanical strength, fine surface finish, high density, and high purity are also the requirements for alumina ceramics used in prosthetics such as hip joints and dental implants.

Other alumina ceramic applications include ceramic armor for bullet-proof vests, balls and rods for grinding media, abrasion-resistant tiles for lining coal and ash transfer lines in power stations, electrical high tension insulators, bioceramics, integrated electronic circuits, vacuum tube envelopes, r-f windows, rectifier housing, integrated circuit packages, and thick and thin film substrates.

Abrasives. Special unground calcined aluminas are used both as feedstock in the manufacture of white fused alumina and as abrasives themselves. Fused alumina production processes and applications have been documented (2,47,48). Graphite electrode, arc-resistance type furnaces are used to melt the calcined alumina in large water-cooled steel shells pots. The optimum unground calcined alumina contains less than 1 μm crystals having a low water adsorptive capacity of about 1% LOI at 1100°C after exposure to 44% rh. This nominally 100 to 325 mesh (149 to 44 μm) free-flowing, sandy alumina provides good coverage of the fused alumina melt. Dust losses are reduced by minimizing the 325 mesh fraction. Controlled water and fluoride additions are claimed to improve whiteness or discoloration by increasing conductivity at the electrode–melt interface (114,115).

Calcined aluminas are also used for polishing applications by mixing into polishing compounds in the form of paste or suspensions. Polishing aluminas are used to alter the surfaces of metals, plastics, glass, and stones in the manufacture of cutlery, automobiles, computers, furniture, eyewear, semiconductors, and jewelry. Polishing aluminas are also used to coat surfaces, such as video tapes (1).

Refractories. Calcined alumina is used in the bond matrix to improve the refractoriness, high temperature strength creep resistance, and abrasion corrosion resistance of refractories (1,2,4,7). The normal, coarse (2 to 5 μm median) crystalline, nominally 100% $\alpha\text{-Al}_2\text{O}_3$, calcined aluminas ground to 95% 325 mesh mesh are used to extend the particle size distribution of refractory mixes, for alumina enrichment, and for reaction with

chemical binders and or clays for reaction bonding. One or more of the calcined aluminas are utilized in amounts to 10⁰ % for special refractories requiring optimum density (4,55).

Unground calcined aluminas are also used as feedstock in the production of fused refractory fibers , bubbles, aggregate, and fused-cast alumina refractories. Abrasive grade calcined alumina is satisfactory for production of all, except for the fused-cast refractories which require a hard-burned Bayer alumina calcined to a low (less than 0.2⁰ % ignition loss after exposure to 44⁰ ° rh) water adsorptive capacity to minimize porosity. Low sulfur requirements for both abrasive and fusion-cast grades of calcined alumina limit the type of fuels that can be used for calcining. The alumina bubbles and Al₂O₃ ·SiO₂ ceramic fibers are used to produce insulating refractories having high porosity and low density structures.

Refractories made using aluminas are used in the iron and steel, chemical and petroleum, ceramics and glass manufacture, minerals processing (cement, lime, etc), public utilities, waste incineration, and power generation industries.

TABULAR ALUMINA

Tabular alumina is a high density, high strength form of α-Al₂O₃ made by sintering an agglomerated shape of ground, calcined alumina. It is available in the form of smooth balls having diameters from 3 to 25 mm and imperfect 19 mm diameter spheres, which are crushed, screened, and ground to obtain a wide variety of graded, granular, and powdered products having various particle size distributions ranging from a top size of 12.7 mm to 325 mesh (44 μm).

Tabular alumina is a recrystallized, sintered α-Al₂O₃ that gets its name from the large, elongated, flat, tabletlike corundum crystals, typically 50 to greater than 400 μm, that develop upon rapid heating of briquettes or balls. It is also characterized by closed spherical porosity (about 5–8⁰ %) entrapped in the large crystals during rapid sintering of the less than 1 μm α-Al₂O₃ crystals. Open porosity is characteristically low, being less than 5⁰ % and typically 2 to 3⁰ % (55).

Tabular alumina processing is similar to that required for making sintered alumina ceramics. Ground calcined alumina is shaped by agglomerating, extruding or pressing, and sometimes using organic binders. The compacted pieces are recrystallized upon sintering at 1873 –2123 K, producing a 3.40–3.65 t m³ bulk-specific gravity product (99.5⁰ % Al₂O₃) having closed spherical porosity, typical of a fully sintered ceramic with secondary crystallization. Impurities typically include about 0.05⁰ % SiO₂, 0.05⁰ % Fe₂O₃, and less than 0.1–0.4⁰ % Na₂O. The lower soda levels are evident in the U.S. products; the higher level in Japanese and European products. Extensive magnetic separation is required to remove iron from the crushed grain to minimize discoloration in ceramic and refractory products. Some processes have been patented (55).

Not all sintered aluminas are tabular Al₂O₃, primarily because sintering aids, such as MgO compounds, are used to achieve densification at lower temperatures and the resultant α-Al₂O₃ crystal size is not large enough to warrant the distinction of tabular Al₂O₃. Such dense sintered alumina grain exhibits poor thermal shock characteristics in comparison with tabular alumina.

Uses

The large α-Al₂O₃ crystals containing closed round pores make tabular alumina an excellent refractory raw material. Advantages include: high refractoriness; high fusion point; good abrasion resistance; excellent hot load strength; low creep; good resistance to chemical attack; high density; low permeability; low reheat shrinkage; good thermal shock resistance; and high purity, minimizing system contamination.

Tabular alumina is the ideal base material for high alumina brick and monolith liners in the metal, ceramic, and petrochemical industries. Applications in the steel industry include alumina slide-grade valves, nozzles, shrouds, weir plates, impact pads, runners, troughs, torpedo car linings, tap holes, high alumina brick, ladle linings, snorkles, and lances. Tabular alumina is universally accepted as the most effective alumina aggregate for manufacture of mullite-bonded and carbon-bonded alumina slide-gate plates used to control the flow of steel from 250 tons and larger ladles.

Tabular alumina also offers advantages over other materials as an aggregate in castables made from calcium aluminate cement as the binder and in phosphate-bonded monolithic furnace linings in all thermal processing industries. Other applications include their use in electrical insulators, electronic components, and kiln furniture. Applications other than refractories and high Al₂O₃ ceramics include molten metal filter media (116), ground filler for epoxy and polyester resins (see FILLERS), inert supporting beds for adsorbents or catalysts, and heat exchange media, among others.

ALUMINATE CEMENT

Refined calcined alumina is commonly used in combination with high purity limestone [1317-65-3] to produce high purity calcium aluminate cement (CAC). The manufacture, properties, and applications of CAC from bauxite limestone, as well as high purity CAC, has been described (104). High purity CAC sinters readily in gas-fired rotary kiln calcinations at 1600–1700 K. CAC reactions are considered practically complete when content of free CaO is less than 0.15⁰ % and loss on ignition is less than 0.5⁰ % at 1373 K.

Table 3 lists the characteristics of CAC mineral constituents that can occur in CAC of varying purities. The primary hydraulic setting cement phase in all CAC grades is CA [12042-68-1], CaO ·Al₂O₃; the main secondary phase in 70⁰ % Al₂O₃ CAC is Ca₂, [12004-88-5], CaO ·2Al₂O₃. CA₂ and C₁₂A₇ [12005-57-1], 12CaO ·7Al₂O₃, occur in minor amounts in the 80⁰ % Al₂O₃ CAC products. The C₁₂A₇ phase reacts rapidly with water to initiate hydraulic bonding and early strength development for rapid mold removal when manufacturing precast shapes. A significant advantage of CAC over Portland cement is its rapid strength development, developing in 24 hours of moist curing, the same proportional strength as Portland cement after 28 days. CA [12005-50-4], CaO ·6Al₂O₃, is the only nonhydrating CAC phase.

Table 3. Characteristics of Calcium Aluminate Cement (CAC) Mineral Constituents^a

Mineral ^b	Chemical composition, wt %		Melting point, K	Molecular weight	Density, g cm ³	Crystal system
	CaO	Al ₂ O ₃				
C	99.8		2843	56.1	3.25–3.38	cubic
C ₁₂ A ₇	48.6	51.4	1633–1663	1387	2.69	cubic
CA	35.4	64.6	1873	158	2.98	
CA ₂	21.7	78.3	2023–2038	260	2.91	monoclinic (triclinic)
C ₂ S ^c	65.1		decomposes	172	3.27	monoclinic
C ₄ AF ^d	46.2	20.9	1688	486	3.77	orthorhombic
C ₂ AS ^e	40.9	37.2	1863	274	3.04	tetragonal
CA	8.4	91.6	2103	668	3.38	hexagonal
α-A		99.8	2324 ^a	102	3.98	hexagonal

^a Ref. 2.

- ^b A = Al₂O₃, C = CaO, F = Fe₂O₃, and S = SiO₂.
- ^c Contains 34.9% SiO₂.
- ^d Contains 32.9% Fe₂O₃.
- ^e Contains 21.9% SiO₂.

Emplaced CAC concrete should be moist cured at temperatures greater than 294 K to avoid explosive steam spalling upon heating after the curing cycle. Below 294 K, an alumina gel forms reducing the permeability of the refractory lining. Low permeability has resulted in severe explosions during heatup of thick (> 10 mm) linings. At temperatures above 300 K, the gel crystallizes into Al(OH)₃ resulting in increased permeability.

CAC castables have rather short working times for placement in comparison to Portland cement concretes. Thus, preconditioning, mixing, and placement of CAC refractory concrete at lower (about 285–290 K) temperatures is favored. This provides sufficiently long placement times to minimize formation defects, which enlarge on drying and firing restricting strength development. Immediately after placement, the temperature of the lining should be increased to above 300 K while being covered with polyethylene plastic sheet or a curing compound to prevent water loss during the moist curing. Hydraulic, dried, and fired strengths increase in proportion to the moist curing time used, but strength development becomes asymptotic after 48–96 hours.

Uses

High purity CA cements are primarily used as binders for high strength refractory castables to form linings up to about 1.0 m thick, as, for example, in iron blast furnaces. Since the 1970s, large monolithic precast CAC castable shapes have found increased usage in a variety of specialty fired shapes that are too expensive to be inventoried.

The high purity CAC finds extensive use as an efficient binder for other aggregates such as fire clays, kaolin, andalusite, kyanite, pyrophyllite, sillimanite, mullite, and refractory grade bauxite, having the added advantage of increasing the refractoriness of some of these aggregates. The many applications cited for tabular alumina in refractories are also common for high purity CAC.

High purity CAC is also used as a steel slag conditioner during ladle refining of steel. CAC clinker in the unground form is added to the steel ladle either prior to or after filling the ladle with steel to form a clean slag, after first removing most of the dirty slag used to protect the steel from oxidation in the transfer ladles. The nominal 50 to 65% Al₂O₃ CAC clinker melts rapidly to provide a protective insulating layer over the molten steel, prevent oxidation, entrap and remove sulfur and metal oxide inclusions from the steel during mixing.

Alumina prices are given in Table 4. Costs of special thermally reactive aluminas run in the \$2.50/kg range because of the high cost of extremely fine grinding. Extra high purity Bayer alumina can run even higher.

Table 4. U.S. Bayer Process Alumina 1989 Year End Prices

Product	Price (\$/kg)
α-aluminum trihydroxide	0.26–0.75
normal Na ₂ O calcined alumina	0.55–0.68
low Na ₂ O calcined alumina	0.68–2.57
tabular alumina	0.86–1.06
calcium aluminate cement (70–80% Al ₂ O ₃)	0.62–0.77

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HYDRATED

The term alumina hydrates or hydrated aluminas is used in industry and commerce to designate aluminum hydroxides. These compounds are true hydroxides and do not contain water of hydration. Several forms are known; a general classification is shown in Figure 1. The most well-defined *crystalline forms* are the trihydroxides, Al(OH)₃; gibbsite [14762-49-3], bayerite [20257-20-9], and nordstrandite [13840-05-6]. In addition, two aluminum oxide–hydroxides, AlO(OH), boehmite [1318-23-6] and diaspora [14457-84-2], have been clearly defined. The existence of several other forms of aluminum hydroxides have been claimed. However, there is controversy as to whether they are truly new phases or structures having distorted lattices containing adsorbed or interlamellar water and impurities.

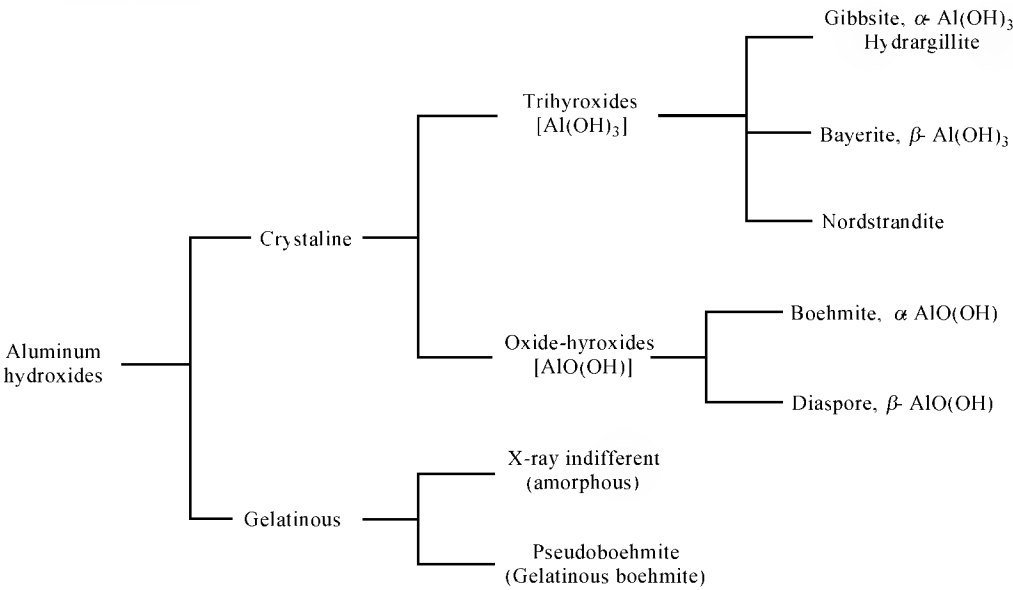


Fig. 1. Classification of aluminum hydroxides.
Courtesy of Aluminum Company of America.

The terms gelatinous alumina or alumina gel cover a range of products in which colloidal hydrated alumina is the predominant solid phase. Structural order varies from x-ray indifferent (amorphous) to some degree of crystallinity. The latter product has been named pseudoboehmite or gelatinous boehmite. Its x-ray diffraction pattern shows broad bands that coincide with the strong reflections of the well-crystallized boehmite.

Crystalline Alumina Hydrates

The mineralogical, structural, physical, and thermodynamic properties of the various crystalline alumina hydrates are listed in Tables 1, 2, and 3, respectively. X-ray diffraction methods are commonly used to differentiate between materials. Density, refractive index, tga, and dta measurements may also be used.

Table 1. Mineralogical Properties of Aluminum Hydroxides

Material	Index of refraction ^a			Cleavage	Brittleness	Mohs' hardness	Luster
	α	β	γ				
gibbsite	1.568	1.568	1.587	(001) perfect	tough	2 ¹ / ₂ –3 ¹ / ₂	pearly vitreous
boehmite	1.649	1.659	1.665	(010)	brittle	3 ¹ / ₂ –4	brilliant pearly
diaspore	1.702	1.722	1.750	(010) perfect		6 ¹ / ₂ –7	

^a The average index of refraction for bayerite is 1.583.

Table 2. Structural Properties of Aluminum Hydroxides

Material	Crystal system ^a	Space group	Unit axis length, nm			Angle	Density g cm ³
			a	b	c		
Al(OH) ₃							
gibbsite	monoclinic ^b	C _{2h} ⁶	0.8684	0.5078	0.9136	94°34'	2.42
bayerite	monoclinic	C _{2h} ⁵	0.5062	0.8671	0.4713	90°27'	2.53
nordstrandite	triclinic	C ₁ ¹	0.5114	0.5082	0.5127	70°16' 74° 0' 58°28'	

<i>AlO(OH)</i>						
boehmite	orthorhombic	D _{2d} ¹⁷	0.2868	0.1223	0.3692	3.01
diaspore	orthorhombic	D _{2d} ¹⁸	0.4396	0.9426	0.2844	3.44

^a Unit cell contains two molecules unless otherwise indicated.

^b Unit cell contains four molecules.

Table 3. Thermodynamic Data for Crystalline Aluminum Hydroxides at 298.15K and 0.1 MPa^a

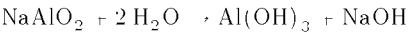
Substance	Molecular weight	Molar vol, cm ³ mol	Δ <i>H</i> ^o _f , kJ mol ^b	Δ <i>G</i> ^o _f , kJ mol ^b	<i>S</i> ^o , J (mol·K) ^b	<i>C_p</i> , J (mol·K) ^b
gibbsite	78.004	31.956	1293.2	1155.0	68.44	91.7
bayerite	78.004		1288.2	1153.0		
boehmite	59.989	19.55	990.4	915.9	48.43	65.6
diaspore	59.989	17.76	999.8	921.0	35.33	53.3

^a To convert MPa to psi, multiply by 145.

^b To convert J to cal, divide by 4.184.

Gibbsite (α-Aluminum Trihydroxide, Hydrargillite). Gibbsite, commonly associated with bauxite [1318-16-7] deposits of tropical regions, is the most important aluminum compound. The gibbsite lattice consists of double layers of hydroxide ions, and aluminum occupies two-thirds of the interstices within the layers. The hydroxyls of adjacent layers are situated directly opposite each other. The layers are somewhat displaced in the direction of the a-axis and the hexagonal symmetry (brucite type) is lowered to monoclinic. The particle size of gibbsite varies from 0.5 to nearly 200 μm depending on the method of preparation. The smaller crystals are composed of plates and prisms whereas the larger particles appear as agglomerates of tabular and prismatic crystals. The basic crystal habit is pseudo-hexagonal tabular.

The usual commercial method of preparation of gibbsite is by crystallization from a supersaturated caustic aluminate, NaAlO₂, solution. Seed gibbsite crystals are used.



Alternatively, neutralization of sodium aluminate [1302-42-7] by CO₂ can be employed.



Crystallization at temperatures of about 40°C results in heavy nucleation and a fine product. At temperatures above 75°C, only crystal growth occurs, giving rise to large, well-crystallized aggregates composed of hexagonal rods and prisms (Fig. 2a).

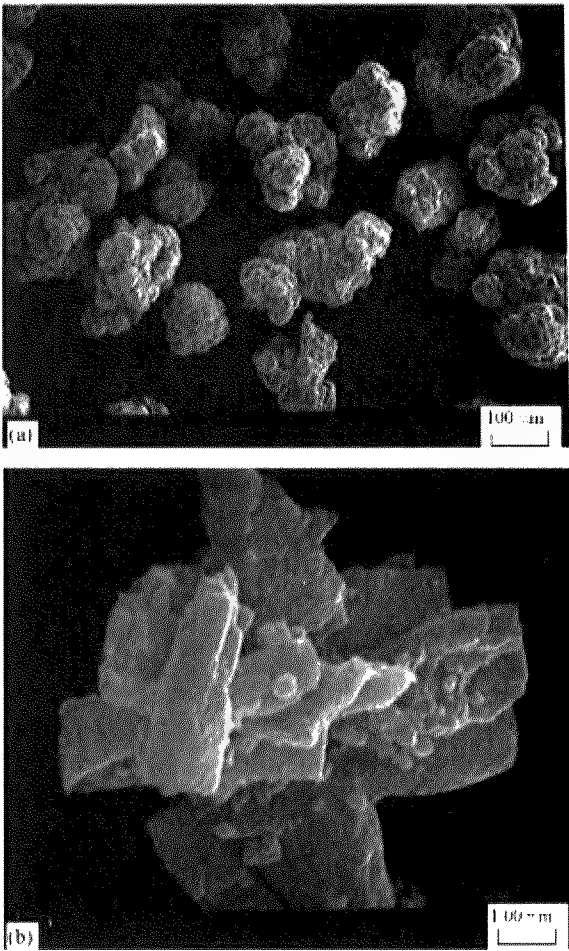


Fig. 2. Aluminum trihydroxides: (a) coarse gibbsite from the Bayer process, ×100; (b) Schumacher bayerite, ×10,000.

Courtesy of Aluminum Company of America.

Gibbsite usually contains several tenths of a percent of alkali metal ions; the technical product, precipitated from a sodium aluminate solution, contains up to 0.3% Na₂O which cannot be washed out even using dilute HCl. Several authors (1,2) suggest that these alkali ions are an essential component of gibbsite structure.

Gibbsite is an important technical product and world production, predominantly by the Bayer process, is more than 50 million metric tons annually. Most (90%) is calcined to alumina [1344-28-1], Al_2O_3 , to be used for aluminum production. The remainder is used by the chemical industry as filler for paper, plastics, rubber, and as the starting material for the preparation of various aluminum compounds, alumina ceramics, refractories, polishing products, catalysts, and catalyst supports.

Bayerite (β -Aluminum Trihydroxide). Bayerite is rarely found in nature. It has been synthesized by several methods: A pure product is prepared by the Schmalz method (3) in which amalgamated aluminum reacts with water at room temperature. Other methods include rapid precipitation from sodium aluminate solution by CO_2 gassing, aging of gels produced by neutralization of aluminum salts with NH_4OH , and rehydration of transition rho alumina.

Unlike gibbsite, pure bayerite can be prepared without any alkali ions and there is evidence that bayerite converts irreversibly to gibbsite in the presence of alkali (Na and K) metal ions. Bayerite does not form well-defined single crystals for proper structural analysis. The most commonly observed growth forms are spindle or hourglass shapes formed by stacking of $\text{Al}(\text{OH})_3$ layers in a direction perpendicular to the basal plane (Fig. 2b). The bayerite lattice is also composed of double layers of OH, but hydroxyl groups of one layer lie in the depressions between the OH positions of the second. This approximately hexagonal close packing results in the higher density of bayerite compared to that of gibbsite.

Bayerite is a commercially available technical product that is produced in small quantities mainly for alumina catalyst manufacture. High purity aluminum [7429-90-5] metal has been converted to bayerite to produce very high purity aluminum oxides.

Nordstrandite. The x-ray diffraction pattern of an aluminum trihydroxide which differed from the patterns of gibbsite and bayerite was published (4) prior to the material, named nordstrandite, being found in nature. The nordstrandite structure is also assumed to consist of double layers of hydroxyl ions and aluminum occupies two-thirds of the octahedral interstices. Two double layers are stacked with gibbsite sequence followed by two double layers in bayerite sequence.

Pure nordstrandite has been prepared (5) by reaction of aluminum, aluminum hydroxide gel, or hydrolyzable aluminum compounds with aqueous ethylenediamine [107-15-3]. However, no commercial production or uses have been reported.

Boehmite (α -Aluminum Oxide-Hydroxide). Boehmite, the main constituent of bauxite deposits in Europe, is also found associated with gibbsite in tropical bauxites in Africa, Asia, and Australia. Hydrothermal transformation of gibbsite at temperatures above 150°C is a common method for the synthesis of well-crystallized boehmite. Higher temperatures and the presence of alkali increase the rate of transformation. Boehmite crystals of 5–10 μm size (Fig. 3) are produced by this method. Fibrous (acicular) boehmite is obtained under acidic hydrothermal conditions (6). Excess water, about 1% to 2% higher than the stoichiometric 15%, is usually found in hydrothermally produced boehmite.

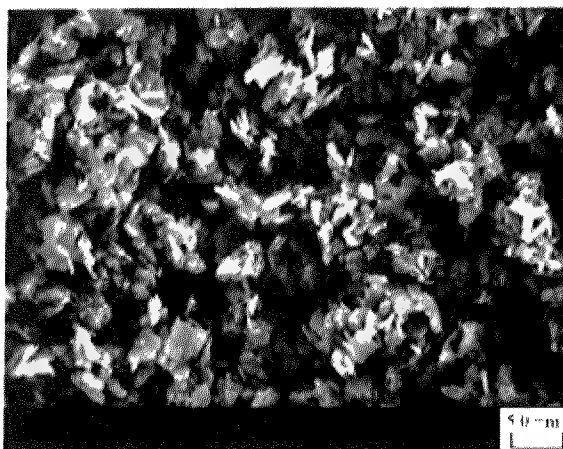


Fig. 3. Aluminum oxide–hydroxide: hydrothermally prepared boehmite, $\times 2,000$.

Courtesy of Aluminum Company of America.

The structure of boehmite consists of double layers in which the oxygen ions exhibit cubic packing. Hydroxyl ions of one double layer are located over the depression between OH ions in the adjacent layer such that the double layers are linked by hydrogen bonds between hydroxyls in neighboring planes. There is some technical production and use of synthetically produced boehmite.

Diaspore (β -Aluminum Oxide Hydroxide). Diaspore, found in bauxites of Greece, China, and the USSR, can also be obtained by hydrothermal transformation of gibbsite and boehmite. Higher ($>200^\circ$) temperatures and pressure (>15 MPa-150bar) are needed for synthesis and the presence of diaspore seed crystals helps to avoid boehmite formation.

In the diaspore structure, the oxygen ions are nearly equivalent, each being joined to another by way of a hydrogen ion and arranged in hexagonal close packing. This arrangement accounts for the higher density of diaspore as compared to boehmite. Although diaspore-containing bauxites and clays have been used for the production of high alumina refractories, no commercial use or large-scale synthesis of diaspore has been reported.

Gelatinous Aluminum Hydroxides

Apart from the crystalline forms, aluminum hydroxide often forms a gel. Fresh gels are usually amorphous, but crystallize on aging and gel composition and properties depend largely on the method of preparation. Gel products have considerable technical use.

The amphoteric behavior of aluminum hydroxide, which dissolves readily in strong acids and bases, is shown in Figure 4. In the pH range of 4 to 9, a small change in pH towards the neutral value causes rapid and voluminous precipitation of colloidal hydroxide which readily forms a gel. Gels are also formed by the hydrolysis of organoaluminum compounds such as aluminum alkoxides (see ALKOXIDES, METAL).

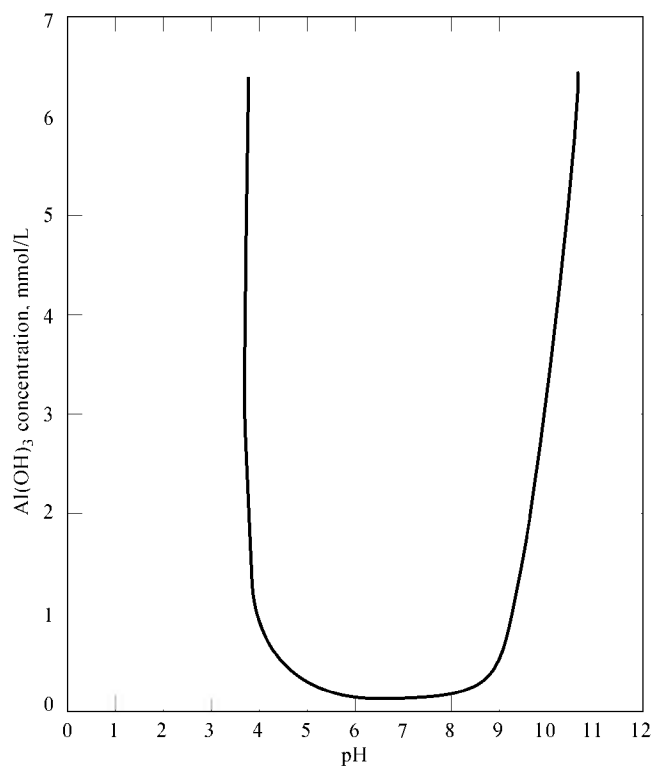
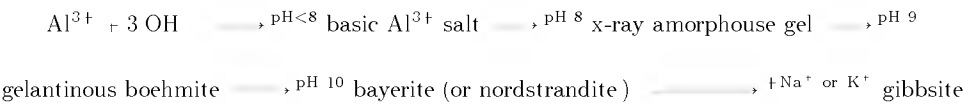


Fig. 4. Amphoteric behavior of Al(OH)₃.

Courtesy of Aluminum Company of America.

Aluminum hydroxide gels contain considerable excess water and variable amounts of anions. Even after prolonged drying at 100–110°C, the water content can be as high as 5 mols H₂O / mol Al₂O₃. The initial precipitated product is usually amorphous (x-ray indifferent), except for material prepared at a pH above 7 or at high temperatures. Gradual transformation to crystalline hydroxide (aging) occurs; the rate is dependent on the OH ion concentration and temperature. Gelatinous boehmite is the first x-ray identifiable crystalline phase and the diffraction pattern shows broad bands that coincide with strong reflections of well-crystallized boehmite (7). In contact with a mother liquor having a pH greater than 7, gelatinous boehmite transforms into crystalline trihydroxides; the rate of transformation increases with pH and temperature. The transformation sequence may be represented by (8)



Gelatinous boehmite, called alumina gel in commercial use, is used in the preparation of adsorbents, desiccants (qv), catalysts, and catalyst supports (see CATALYSTS, SUPPORTED). A significant amount is used in pharmaceutical preparations.

Phase Relations in the Al₂O₃–H₂O System

Under equilibrium vapor pressure of water, the crystalline trihydroxides, Al(OH)₃ convert to oxide–hydroxides at above 100°C (9,10). Below 280°–300°C, boehmite is the prevailing phase, unless diaspor seed is present. Although spontaneous nucleation of diaspor requires temperatures in excess of 300 °C and 20 MPa (200 bar) pressure, growth on seed crystals occurs at temperatures as low as 180 °C. For this reason it has been suggested that boehmite is the metastable phase although its formation is kinetically favored at lower temperatures and pressures. The ultimate conversion of the hydroxides to corundum [1302-74-5], Al₂O₃, the final oxide form, occurs above 360°C and 20 MPa.

Several nonequilibrium forms of aluminum oxides have been observed (11,12) in hydrothermal experiments at low water vapor pressures in the temperature region of 300–500°C. The KI–Al₂O₃ form, also known as tondite [12043-15-1], Al₂O₃ · 1/5 H₂O, is characterized by a distinct x-ray diffraction pattern.

Production

Aluminum hydroxides are technically the most widely used members of the alumina chemicals family. The most important source of aluminum hydroxides is the bauxite refining plant for alumina production. A small amount of somewhat purer aluminum hydroxide is produced by the Sinter process.

The operating conditions and practices of alumina refining plants are generally geared to the production of a single grade of metallurgical alumina and the hydroxide has rather limited chemical uses in the form produced for this conversion. Variations in particle size, purity, and other properties are generally needed before the hydroxide can be utilized for chemical applications. Thus a part of the aluminate liquor is diverted to special purpose crystallization vessels. The crystallized product is filtered, washed thoroughly using clean hot water to remove adhering caustic liquor, and dried. Care has to be exercised in the drying operation to avoid exposure to high (>150°C) temperatures which could cause dehydration and thus affect such properties as surface activity and dissolution rate in acids and alkali. Several commercial grades of aluminum hydroxide are produced. The properties of some grades are given in Table 4.

Table 4. Properties of Commercial Grade Aluminum Hydroxides

Property	Normal coarse grade ^a	Normal white grade ^b	Ground ^c	Fine precipitated ^d
Al ₂ O ₃ , wt %	65.0	65.0	65.0	64.7
SiO ₂ , wt %	0.012	0.01	0.02	0.04
Fe ₂ O ₃ , wt %	0.015	0.004	0.03	0.01
Na ₂ O (total), wt %	0.40	0.15	0.30	0.45
Na ₂ O (soluble), wt %	0.05	0.05	0.05	0.1–0.25

LOI at 1200°C, wt % ^e	34.5	34.5	34.5	34.5
moisture at 100°C, wt %	0.1	0.1	0.4	0.3–1.0
specific gravity	2.42	2.42	2.42	2.42
bulk density (loose), g cm ³	1.2–1.4	1.0–1.1	0.7–1.25	0.13–0.22
surface area, m ² g	0.1	0.15	2–4	6–8
color	off-white	white	off-white	white
refractive index	1.57	1.57	1.57	1.57
Mohs' hardness	2.5–3.5	2.5–3.5	2.5–3.5	2.5–3.5
<i>Particle size, cumulative wt %</i>				
retained 100 mesh 149 μm	5–20	0–1		
retained 200 mesh 74 μm	65–90	5–15		
retained 325 mesh 44 μm	90–98	30–65	1–2	0.1–0.2
passing 325 mesh 44 μm	2–10	35–70	98–99	99.8
median particle size, μm			6.5–9.5	0.6

^a Alcoa C-30.
^b Alcoa C-31.
^c Alcoa C-330.
^d Alcoa Hydral 710.
^e Loss on ignition.

Hydroxide grades can be surface-treated to modify dispersion behavior and rheological properties. The most widely used surface coating agents are stearic acid [57-11-4] and stearates. Additionally, compounds from the silane group have been used as coupling agents to give improved adhesion to polymers when the hydroxide is used as a filler.

Normal Coarse Grade Bayer Hydrate. The normal coarse grade Bayer hydrate has the lowest cost. It corresponds to the usual Bayer plant product produced for conversion to metallurgical alumina. Traditionally, the American Bayer product is coarser than the European product; chemical compositions are nearly identical. The hydroxide is approximately 99.5% pure. Principal impurities are soda, Fe₂O₃, SiO₂, and small amounts of TiO₂. Organic impurities originating from bauxite impart an off-white or yellowish color to the hydroxide. This low cost commodity grade material is widely used for the manufacture of alum and other aluminum chemicals.

White Hydroxide. The soda sinter process applied to bauxite or bauxite residue produces a hydroxide that is completely free from organic coloring matter and is very white. A value of more than 95% is obtained on the GE brightness scale relative to TiO₂ as followed in the paper (qv) industry. This compares to about 70% on the same scale for the normal Bayer product. The white hydroxide is preferred in the paper, toothpaste, and artificial marble industries.

Ground Hydroxides. Many applications of aluminum hydroxides require smaller particle sizes obtained mostly by grinding the dry hydroxide from the refining plant, followed, if necessary, by size classification. Types of grinding equipment include: ball and jar mills (sometimes ceramic lined and using ceramic balls to avoid iron contamination), vibrating mills, disc mills, and air or steam jet pulverizers. Aluminum hydroxide is relatively easy to grind; consistency of particle size distribution is desirable in the production and applications of ground hydroxides. Direct precipitation of a fine hydroxide is possible, but is not widely practiced because filtration, washing, and drying of fine products are relatively more difficult. Ground hydroxides are used extensively as fire retardant fillers in plastics (see FLAME RETARDANTS).

Low Soda Hydroxide. The Na₂O content of normal Bayer hydroxide is around 0.2–0.4%, 0.1% of which can be removed by thorough washing. The remaining soda is trapped within the hydroxide crystal. Experience shows that the occluded soda content is reduced when crystallization is carried out under low alumina-supersaturation conditions and at relatively higher temperatures (80–95°C). Soda contents as low as 0.05% Na₂O can be obtained by this procedure. However, these conditions also reduce hydroxide yield and thus increase the production cost. Low soda aluminum hydroxide is generally employed in the production of aluminas for the ceramics industries.

Extra-Fine Precipitated Hydroxide. Very fine (<1 μm-diameter) particle size hydroxide is produced by precipitation under carefully controlled conditions using specially prepared hydroxide seed. Precipitation is usually carried out at low (30–40°C) temperatures causing massive nucleation of fine, uniform hydroxide particles (Fig. 5). Tray or tunnel type dryers are used to dry the thoroughly washed filter cake to a granular product which is easily pulverized to obtain the fine hydroxide. Alternatively, the washed product is spray dried. Precipitation from an organic-free aluminate liquor, such as that obtained from the soda-sinter process, yields a very white product. The fine precipitated hydroxide is used by the paper and plastic industries as fillers.

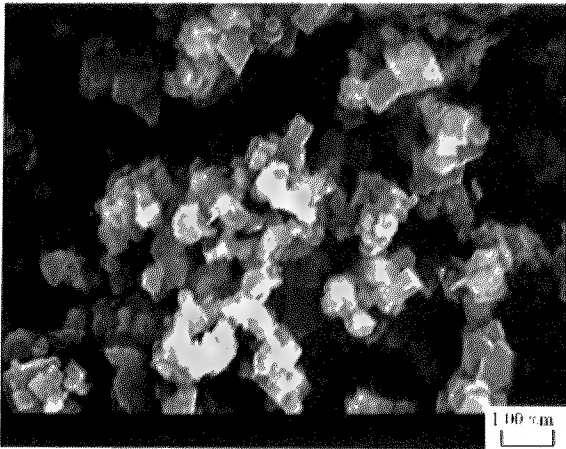


Fig. 5. Fine precipitated aluminum hydroxide, × 10,000.

Courtesy of Aluminum Company of America.

Production of Other Aluminum Hydroxides. Commercial production of gelatinous aluminum hydroxide involves the neutralization of aluminum sulfate [10043-01-3] or ammonium alum [7784-25-0] by ammonia or sodium hydroxide. Neutralization of a sodium aluminate solution by acids, NaHCO₃, or CO₂ has also been used. The gelatinous product is difficult to filter and wash, and the product is often aged to improve washability. The filter cake is either dried and pulverized, or directly extruded and cut to the desired shape and size, and then dried. Spray drying has also been used. The dried powder may be agglomerated to yield a spherical product or pressed into pellets. Drying and dehydration in a hot oil bath also has been used to produce spherical particles. Rate, temperature, pH variation, agitation during neutralization, and the subsequent aging all play significant roles in the development of

reproducible properties of the final product. Gelatinous aluminum hydroxides are extensively used in the preparation of adsorbent and catalytic aluminas. They are also used in the pharmaceutical industry and in the manufacture of printing inks.

The Ziegler process involves the formation of aluminum alkoxides at an intermediate stage (see ALCOHOLS, HIGHER ALIPHATIC). Hydrolysis of the alkoxides produces aluminum hydroxide having pseudoboehmite structure. The hydroxide product is further processed to remove residual alcohols and then dried. The chemical purity is generally high; the most significant contaminant is sometimes TiO₂. Catalytic applications have been the principal market for this product because of its higher purity.

Commercial production of bayerite is relatively small and employs CO₂ neutralization of caustic aluminate liquor obtained from either Bayer or sinter processes. The product obtained is about 90% crystalline bayerite having small amounts of gibbsite, pseudoboehmite, and amorphous aluminum hydroxides.

Shipping and Analysis

Shipping of aluminum hydroxide powders is usually in paper bags of 10 to 25 kg size. Bulk shipment by road or rail wagons is also common. Aluminum hydroxides are not hygroscopic, but could be dusty and precautions against dust inhalation should be taken during handling.

Many of the procedures used for technical analysis of aluminum hydroxides are readily available from the major producers of aluminum hydroxides.

Phase Composition. Weight loss on ignition (110°–1200°C) can differentiate between pure (34.5% Al(OH)₃) trihydroxides and oxide–hydroxides (15% Al(OH)₃). However, distinction between individual trihydroxides and oxide –hydroxides is not possible and the method is not useful when several phases are present together. X-ray powder diffraction is the most useful method for identifying and roughly quantifying the phase composition of hydroxide products.

Thermal Analyses. Thermal analysis often complements x-ray data in providing information on phase composition. The thermal behavior of aluminum hydroxides is particularly important in filler type applications.

Particle Size and Shape. Particle size information is important for many aluminum hydroxide applications. Sieve analysis, both dry and wet, is commonly used in the 20 μm (using micro-sieves) to 200 μm size range. Sizes in the 2–200 μm range have been analyzed by light microscopy, sedimentation (eg, Andreasen pipette, sedimentation balances, Sedigraph instrument), Coulter Counter, and MicroTrac instruments. Electron microscopy is the only reliable procedure for characterizing particles below 2-μm size. Scanning electron microscopy has proved useful in obtaining information on particle shape and the relation to behavior in many applications.

Alkalinity (Soluble Soda) Determination. The surface alkalinity or soluble or leachable soda is determined by making a fixed weight percent slurry in water and determining the alkalinity of the solution by pH measurement or acid titration. Sodium ion-sensitive electrodes have been investigated.

Whiteness and Brightness. Photometric instruments, originally developed by the paper industry, are used for these measurements. Values are compared against standard white pigments such as BaSO₄, TiO₂, or MgO.

Chemical Analysis. Chemical impurities commonly analyzed include Na₂O, Fe₂O₃, and SiO₂. The hydroxide is first dissolved in boiling concentrated HCl. Atomic absorption methods have replaced older colorimetric procedures.

Other Measurements. Other tests include free moisture content, rate of dissolution and undissolved residue in acids and alkali, resin and plasticizer absorption, suspension viscosity, and specific surface area. Test procedures for these properties are developed to satisfy application-related specifications.

Economic Aspects

World aluminum hydroxide production capacity was nearly 50 million metric tons in 1988. Approximately 92% of the hydrated alumina produced was converted to metallurgical alumina. About 90% of world production came from the Bayer process; the remaining came from Sinter, Ziegler, and gel processes. Although many alumina plants possess the capability to make the normal Bayer-grade hydroxide, specialty grade aluminum hydroxides for the chemical industry are generally produced in alumina refining plants dedicated to nonmetallurgical alumina products. Table 5 lists these plants and their capacities.

Table 5. Location and Capacities of Chemical Grade Alumina Production Facilities

Company	Location	Country	Al ₂ O ₃ capacity, t × 10 ³ yr
Alcan	Vaudreuil, Quebec	Canada	150
	Bauxite, Arkansas	United States	300
Aluminum Company of America	Point Comfort, Texas	United States	200
Aluminum Company of America (Brazil)	Pocos De Caldas	Brazil	120
BACO Chemicals	Burntisland	United Kingdom	120
Martinswerk	Bergheim	Germany	350
Pechiney	Salinders	France	250
Reynolds	Corpus Christi, Texas	United States	100
Shandong Alumina	Shandong	China	150
Showa Aluminum	Yokohama	Japan	200
Sumitomo Chemicals	Kikumoto	Japan	250
VAW	Schawndorf	Germany	100

Approximately 600,000 metric tons of aluminum hydroxides were used in chemical applications in the United States in 1988: 40% as fillers, 45% for the production of aluminum chemicals, and 15% for various other uses. Carpet backing was the principal filler type application followed by polyester products.

The price of aluminum hydroxides ranged from \$0.40 to \$1.50 /kg in 1988 depending upon processing and purity. The white grades were priced from 1.5 to 2 times higher than the usual off-white Bayer hydroxide. Pharmaceutical-grade gel hydroxides were at the top of the price range followed by Ziegler process pseudoboehmite.

Bayer aluminum hydroxides in most grades are sold by all major U.S. alumina producers. Other firms offering aluminum hydroxide fillers probably operate reprocessing facilities to grind or otherwise treat hydroxide obtained from the primary producers. Countries exporting small amounts to the United States are Japan, Germany, Canada, and the UK.

Health and Safety Information

Aluminum hydroxides are minimally absorbed by the body and LD₅₀ values for ingestion are unavailable. Death upon ingestion occurs from intestinal blockage rather than systemic aluminum toxicity (13). It is only as a fine particulate suspended in air that aluminum hydroxides may gain entry (via the lungs) into the body in amounts of physiological significance. Evidence collected among workers in the alumina refining industry has failed to show any

effect of aluminum hydroxide dust on the lungs. However, in recognition of the possible adverse effects of long term exposure to alumina dusts, threshold limit values have been established by the ACGIH (14) as follows: 10 mg m³ TLV–TWA and 20 mg m³ TLV–STEL. Aluminum hydroxide [21645-51-2] and aluminum hydroxide oxide [24623-77-6] are reported in EPA TSCA inventory.

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ALUMINUM SULFATE AND ALUMS

Aluminum sulfate octadecahydrate [7784-31-8], $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$, and its aqueous solutions are used primarily in the paper (qv) industry for sizing and as a flocculating agent in water (qv) and wastewater treatment. This material is often called papermakers' alum or alum. Because this salt is precipitated from aqueous solution, aluminum sulfate hydrate [17927-65-0], $\text{Al}_2(\text{SO}_4)_3 \cdot n\text{H}_2\text{O}$, can have variable composition and is sometimes referred to as cake alum or patent alum. The solid commercial hydrate, generally written as the 18-hydrate, is typically dehydrated to correspond to from 17.0–17.5% Al_2O_3 where $n = 13\text{--}14$ (1,2). This dehydrated form is called dry alum, ground or lump. Aluminum sulfate solutions are typically 7.5–8.5% Al_2O_3 and are known as liquid alum.

Confusion arises in the nomenclature of alum because double salt compounds, $\text{M(I)Al}(\text{SO}_4)_2$, where M is in the +1 oxidation state, have also traditionally been called alums. In particular, potassium aluminum sulfate [15007-61-1] $\text{KAl}(\text{SO}_4)_2 \cdot n\text{H}_2\text{O}$, is referred to as ordinary alum or potash alum.

Anhydrous aluminum sulfate [10043-01-3], $\text{Al}_2(\text{SO}_4)_3$, is a specialty item used in food applications.

Properties

Over 50 acidic, basic, and neutral aluminum sulfate hydrates have been reported. Only a few of these are well characterized because the exact compositions depend on conditions of precipitation from solution. Variables such as supersaturation, nucleation and crystal growth rates, occlusion, nonequilibrium conditions, and hydrolysis can each play a role in the final composition. Commercial dry alum is likely not a single crystalline hydrate, but rather it contains significant amounts of amorphous material.

Hydrates. Aluminum sulfate hydrates, $\text{Al}_2(\text{SO}_4)_3 \cdot n\text{H}_2\text{O}$, where n ranges from 0 to 27 have been reported (3–6). Relative decreasing vapor pressure studies indicate the presence of an octadecahydrate, hexadecahydrate, dodecahydrate, dihydrate, and the anhydrous salt, assuming that basic aluminum sulfates are not formed during the dehydration (3).

Thermal analysis of the dehydration of $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ shows loss of 15 moles of water between 40°C and 250°C and 3 moles between 250°C and 420°C (7). Heating rate can affect the product. Although rapid heating can fuse hydrated aluminum sulfate containing >35% water and puff material containing 25–35% water, these problems do not occur during slow heating in an agitated bed. An aluminum sulfate hydrate can dissolve in its water of crystallization during heating.

Solubility. The aqueous solubility of a typical commercial aluminum sulfate, $\text{Al}_2(\text{SO}_4)_3 \cdot n\text{H}_2\text{O}$, where $n = 14\text{--}18$, is shown compared to the solubility of the octadecahydrate in Table 1 (2,8). Differences in solubilities probably result from small amounts of impurities such as iron, and the slight excess of Al_2O_3 base present in technical grade commercial aluminum sulfate hydrate.

Table 1. Aqueous Solubility of Aluminum Sulfate Hydrates, $\text{Al}_2(\text{SO}_4)_3 \cdot n\text{H}_2\text{O}$

Temperature, °C	Solubility, $\frac{\text{g anhydrous salt}}{100 \text{ g sat'd soln}}$	
	$n = 18^a$	$n = 14\text{--}18^b$
0	27.5	23.9
10	27.6	25.1
20		26.6
25	27.8	
30	28.0	28.8
35	28.4	
40	28.8	31.4
50	29.9	34.2
60	31.0	37.2
70	32.8	39.8
80		42.2
82	36.6	
90		44.7
95	41.9	
100		47.1
103	46.9	

^a Ref. 8.
^b Commercial hydrate data from ref. 2.

Aqueous solutions of aluminum sulfate can hydrolyze at temperatures of about 150°C (9) resulting in products having a formula such as $3\text{Al}_2\text{O}_3 \cdot 4\text{SO}_3 \cdot 9\text{H}_2\text{O}$, which is structurally related to alunite [12588-67-9], $\text{K}_2\text{Al}(\text{SO}_4)_4(\text{OH})_{12}$ (10).

Crystallization. Acidified aluminum sulfate solutions can be supercooled 10 °C or more below the saturation point. However, once nucleation begins, the crystallization rate is rapid and the supersaturated solution sets up. The onset of nucleation in a gently stirred supersaturated solution is marked by the appearance of silky, curling streamers of microscopic nuclei resulting from orientation effects of hydraulic currents on the thin, platelike crystals. Without agitation, nucleation in an acidified solution, in glass tubes, can yield extended crystalline membranes of such thinness to exhibit colors resulting from optical interference.

Other Properties. The formula weight for the octadecahydrate is 666.45 and its specific gravity is 1.69 at 17°C (11). Other physical properties such as percentage of Al_2O_3 in alum liquor vs specific gravity at 15.6°C, pH as a function of alum concentration, heat evolved on mixing $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ and water, viscosity of aqueous alum solutions as a function of temperature, crystallization temperature of $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ as a function of the alum concentration, and the boiling point of alum solutions as a function of the alum concentration have been reported (2,11). Representative data are given in Tables 2 and 3. The ACGIH threshold limit value TWA is 2 mgAl / m³ (12) and the oral, mouse LD₅₀ is 6207 mg / kg (12).

Table 2. Aluminum Sulfate Solution Properties

Composition, % Al_2O_3	pH ^a	Specific gravity at 15.6°C ^b	Crystallization temperature, °C ^c
2.0	2.9		4
4.0	2.4		6
5.0		1.182	
5.5		1.204	
6.0	2.1	1.222	8
6.5		1.246	
7.0		1.269	11
7.5		1.291	
8.0	1.9	1.314	15
8.2			16
8.4			14
8.5		1.337	
8.6			8
8.8			29

^a Values are for neutral alum solutions; commercial alum liquor contains excess H_2SO_4 , and values run about 0.5 pH units lower; slightly basic alum solutions, some excess Al_2O_3 , have values of about 0.5 pH units higher.

^b Values depend on alum producing point; for example, at 8.0% Al_2O_3 , range can be 1.311 to 1.334.

^c Values are for the 18-hydrate, $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$.

Table 3. Dissolution Time of Dry Alum, $\text{Al}_2(\text{SO}_4)_3 \cdot 14.3\text{H}_2\text{O}$, and Heat Evolved on Mixing

Dry alum added to 378.5 L H_2O , kg	Dissolving time, min at			Heat evolved on mixing at 18°C, kJ ^a
	4°C	16°C	38°C	
91	9	6	2	8
181	15	9	3	18
272	25	15	5	26

^a To convert J to cal, divide by 4.184.

Uses and Economic Aspects

The pulp and paper industry and potable and wastewater treatment industry are the principal markets for aluminum sulfate. Over half of the U.S. aluminum sulfate produced is employed by the pulp and paper industry. About 37% is used to precipitate and fix rosin size on paper fibers, set dyes, and control slurry pH. Another 16% is utilized to clarify process waters. The alum sold for these purposes is usually liquid alum. It is frequently acidic as a result of a slight excess of H_2SO_4 . Aluminum sulfate consumption by the pulp and paper industry is projected to remain constant or decline slightly in the near term because of more efficient use of the alum and an increased use of alkaline sizing processes (13).

Aluminum sulfate is used as a flocculating agent or coagulant in water and wastewater treatment (see FLOCCULATING AGENTS). This use, excluding the 16% employed in process water treatment by the pulp and paper industry, accounts for 44% of U.S. consumption. Alum sold to municipalities in the United States is required by the American Water Works Association (AWWA) to be basic as a result of a slight excess of Al_2O_3 . When alum is added to water, positively charged hydrated or hydroxylated aluminum ions neutralize and adsorb negatively charged colloidal and suspended matter in the water causing the material to floc and settle out (14). Increased use of organic polymeric coagulants and combinations of organic and inorganic coagulants has decreased somewhat the aluminum sulfate market. Polyaluminum chloride, basic aluminum sulfate (15–17), and a more recent basic aluminum chlorosulfate (18,19) are all effective coagulants. The near term market for aluminum sulfate in water treatment is projected to remain flat.

Other uses for aluminum sulfate include tanning (see LEATHER), and as a pH stabilizer, cement (qv) hardening accelerator, mordant in dyeing (see DYES AND DYE INTERMEDIATES), anticaking agent, fire extinguisher, and as a flame retardant additive, a use which dates to the early Egyptians (see FLAME RETARDANTS). Wood (qv) and cellulose (qv) treatment, catalysis (qv), and pharmaceutical and cosmetic applications are known (see COSMETICS AND PHARMACEUTICALS). Some more recent Japanese literature suggests uses as an absorbent for odor and gases (20). Alum is effective in reducing the phosphate content of sewage and wastewater and in combating the eutrophication of lakes (21,22). USSR literature cites uses in drilling muds (23).

Aluminum sulfate is a starting material in the manufacture of many other aluminum compounds. Aluminum sulfate from clay could potentially provide local sourcing of raw materials for aluminum production. Processes have been studied (24) and the relative economics of using clay versus bauxite have been reviewed (25). It is, however, difficult to remove impurities economically by precipitation, and purification of aluminum sulfate by crystallization is not practiced commercially because the resulting crystals are soft, microscopic, and difficult to wash effectively on a production scale (26–28).

In the United States, 19 companies produced aluminum sulfate in 83 plants in 1991. The total 1989 U.S. production was 1100 thousand metric tons on a 17% Al_2O_3 basis. In Western Europe, 720 thousand metric tons, on a 17.0–7.5% Al_2O_3 basis, were produced by 39 companies in 1989. Over 14 companies made 836 thousand metric tons of aluminum sulfate on a 14% Al_2O_3 basis in Japan in 1990.

Aluminum sulfate hydrate is marketed as material commercial or technical grade containing a maximum of 0.5% Fe_2O_3 . The commercial grade is available as a dry ground product containing from 17.0 to 17.5% Al_2O_3 , 57–59% $\text{Al}_2(\text{SO}_4)_3$, and as an aqueous solution containing from 7.5 to 8.5% Al_2O_3 . Pricing data and U.S. annual production statistics may be found in Tables 4 and 5, respectively (13).

Table 4. Annual U.S. Prices for Aluminum Sulfate, Dollars per Metric Ton^a

Year	Commercial grade		Iron-free grade	
	Dry, ground ^b	Liquid ^c	Dry ^d	Liquid ^e
1960	44		84	
1965	49		84	
1970	59	48	92	
1975	109	68	154	108
1980	183	111	237	182
1985	259	160	440	248

1990	254	160	358	287
^a Ref. 13.				
^b Price basis, 1960–1970: bulk, carlots, works, freight equalized; 1980–1984: bags, carlots, works, freight equalized, as 17° o Al ₂ O ₃ .				
^c Prices basis, 1970: dry basis; 1975–1984: tanks, Northeast, works, freight equalized, as 17° o Al ₂ O ₃ .				
^d Price basis, 1960–1970: bags, carlots, works, freight equalized; 1975–1990: bags, carlots, works, freight equalized, as 17° o Al ₂ O ₃ .				
^e Price basis: tanks, works, freight equalized, as 17° o Al ₂ O ₃ .				

Table 5. Annual U.S. Production of Aluminum Sulfate on a 17.0% Al₂O₃ Basis in Thousands of Metric Tons^a

Year	Grade		Total ^b
	Commercial	Iron-free	
1960	797	47	848
1965	964	54	1022
1970	1080	64	1149
1975	1035	228	1268
1980	1167	106	1273
1985	1092	96	1188
1989	1128	115	1243

^a Ref. 13.
^b Total includes 4,000 metric tons of municipal production in 1960 and 1965; 5,000 metric tons in 1970 and 1975.

Manufacture

In the United States, aluminum sulfate is usually produced by the reaction of bauxite or clay (qv) with sulfuric acid (see SULFURIC ACID AND SULFUR TRIOXIDE). Bauxite is imported and more expensive than local clay, generally kaolin, which is more often used. Clay is first roasted to remove organics and break down the crystalline structure in order to make it more reactive. This is an energy intensive process. The purity of the starting clay or bauxite ore, especially the iron and potassium contents, are reflected in the assay of the final product. Thus the selection of the raw material is governed by the overall economics of producing a satisfying product.

The optimum conditions for roasting the clay and the optimum strength (30–60° o) of the sulfuric acid used depend on the particular raw material. Finely ground bauxite or roasted clay is digested with sulfuric acid near the boiling point of the solution (100–120°C). The clay or bauxite-to-acid ratio is adjusted to produce either acidic or basic alum as desired and solids are removed by sedimentation. If necessary, the solution can be treated to remove iron. However, few, if any, of the many methods claimed to be useful for iron removal have been used industrially (29). Instead, most alum producers prefer to use raw materials that are naturally low in iron and potassium.

The clear supernatant solution is decanted and sold in liquid form or concentrated to approximately 61.5° Bñ and then allowed to solidify to form blocks that are crushed, ground, and graded. A typical analysis for the dry product is: total Al₂O₃, 17.0–17.5° o; Fe₂O₃ <0.5%; water of composition 42–43° o; insoluble <1.0%. Liquid alum contains 7.5–8.5° o Al₂O₃. At concentrations >8.5% Al₂O₃, crystallization of the solution may occur.

The iron-free grade of aluminum sulfate hydrate contains less than 0.005° o iron as Fe₂O₃. It is manufactured from pure alumina trihydrate [12252-70-9] Al₂O₃·3H₂O, rather than from bauxite or clay. Although a technical or commercial grade alum can be treated to remove iron, such processes are not sufficiently economical to meet the requirements for the iron-free grade (29). The presence of iron can cause discoloration or staining of the product employing the aluminum sulfate.

Other Alums

The word alum is derived from the Latin *alumen*, which was applied to several astringent substances, most of which contained aluminum sulfate (20). Unfortunately, the term alum is now used for several different materials. Papermakers' alum or simply alum refers to commercial aluminum sulfate. Common alum or ordinary alum usually refers to potash alum which can be written in the form K₂SO₄·Al₂(SO₄)₃·24H₂O, or it can refer to ammonium alum, ammonium aluminum sulfate. The term is also applied to a whole series of crystallized double sulfates [M(I)M'(III)(SO₄)₂·12H₂O] having the same crystal structure as the common alums, in which sodium and other univalent metals may replace the potassium or ammonium, and other metals may replace the aluminum. Even the sulfate radical may be replaced, by selenate, for example. Some examples of alums are cesium alum [7784-17-0], CsAl(SO₄)₂·12H₂O; iron alum [13463-29-1], KFe(SO₄)₂·12H₂O; chrome alum [7788-99-0], KCr(SO₄)₂·12H₂O; and chromoselenic alum [17855-06-0], KCr(SeO₄)₂·12H₂O.

Pseudoalums are a series of double sulfates, such as iron(II) aluminum sulfate [22429-82-9], FeSO₄·Al₂(SO₄)₃·24H₂O, containing a bivalent metal ion in place of the univalent element of ordinary alums. These pseudoalums have different crystal structures from those of the ordinary alums.

In industrial practice it is generally the aluminum content of alums that is important. Because aluminum sulfate is widely available, other alums are more specialty items and are no longer produced in quantities comparable to those of aluminum sulfate (14).

Ammonium Aluminum Sulfate. Ammonium aluminum sulfate [7784-26-1], NH₄Al(SO₄)₂·12H₂O, is also known as ammonium alum or ammonia alum. It is a colorless crystal having a strong, astringent taste; formula weight 453.33; mp, 94.5 °C; sp gr 1.64; and solubility of 12.0 g per 100 mL H₂O at 20°C (8). It is soluble in dilute acid and insoluble in alcohol. The material dehydrates at about 250 °C (30) to porous, dry ammonium alum [7784-25-0], NH₄Al(SO₄)₂, formula weight 237.14, which is also called dried or burnt alum. Decomposition of the anhydrous material begins at 280 °C and γ-Al₂O₃ is formed between 1000 and 1250°C.

Ammonium alum is manufactured by crystallization from a mixture of ammonium sulfate and aluminum sulfate or by the treatment of aluminum sulfate and sulfuric acid with ammonia gas. Ammonium alum is used in medicine, as a mordant in dyeing, dressing furs in tanning, paper sizing, and water purification. It can be used in baking powders (see BAKERY PROCESSES AND LEAVENING AGENTS). It has also been used as the starting material to produce finely powdered aluminum oxide for the manufacture of synthetic corundum gems (see GEMS, SYNTHETIC) (14).

Ammonium alum sold at \$0.77 to 1.21 kg in 1990 (31).

Potassium Aluminum Sulfate. Potassium aluminum sulfate [7784-24-9], KAl(SO₄)₂·12H₂O, is a white, astringent crystal known as potassium alum, ordinary alum, or potash alum. Its formula weight is 474.39; mp 92.5 °C; sp gr 1.75; and solubility 11.4 g per 100 mL H₂O at 20°C (8). It is soluble in dilute acid and insoluble in alcohol. It dehydrates at about 200 °C to porous desiccated potassium alum [10043-67-1], KAl(SO₄)₂, a dried or burnt alum, which has a formula weight of 258.20.

Potassium alum is manufactured by treating bauxite with sulfuric acid and then potassium sulfate. Alternatively, aluminum sulfate is reacted with potassium sulfate, or the mineral alum stone, alunite, can be calcined and leached with sulfuric acid. Alunite is a basic potassium aluminum sulfate [1302-91-6], $K_2Al(SO_4)(OH)_{12}$, sp gr 2.58–2.75.

Potassium alum, which also occurs naturally as the mineral kalinite [7784-24-9], $KAl(SO_4)_2 \cdot 12H_2O$, sp gr 1.75, is used in tanning skins, as a mordant in dyeing, and in the pharmaceutical and cosmetic industries (see PHARMACEUTICALS; COSMETICS). It is used as a styptic pencil and as a hardening agent and set accelerator for cement and plaster. The ACGIH threshold limit value TWA is 2 mgAl m⁻³ (12).

Potassium alum sold at \$0.77 to \$1.21 kg in 1990 (30).

Sodium Aluminum Sulfate. Sodium aluminum sulfate [7784-28-3], $NaAl(SO_4)_2 \cdot 12H_2O$, known as sodium alum, is a colorless crystal having an astringent taste; mp 61°C; and sp gr 1.675. It is the most water soluble alum: 75 g per 100 mL H₂O at 20°C (8). It is soluble in dilute acid and insoluble in alcohol.

Sodium alum occurs naturally as the mineral mendozite. Commercially, it is produced by the addition of a sodium sulfate solution to aluminum sulfate. Small amounts of potassium sulfate, sodium silicate, and soda ash can be added to improve product handling and performance. After adjustment of the ratio of aluminum sulfate to sodium sulfate, water is evaporated to give a hard cake in the cooling pans. This cake is further heated in roasters and ground to a fineness of 99° through a 100-mesh (~150 μm) sieve.

In the United States, sodium aluminum sulfate is used as a leavening agent in baking applications. Sodium aluminum sulfate, food grade, sold at \$1.17 kg in 1990.

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POLYALUMINUM CHLORIDES

Aluminum chloride hydroxide [1327-41-9], [10284-64-7], $\text{AlCl}(\text{OH})_2$ [14215-15-7], $\text{AlCl}_2(\text{OH})$, products, commonly known as polyaluminum chlorides (PAC), are used for a wide variety of industrial applications. Other names for PAC are basic aluminum chloride, polybasic aluminum chloride, aluminum hydroxychloride, aluminum oxychloride, and aluminum chlorohydrate. The presence of polymeric, aluminum-containing cations, the distribution of which can differ greatly, typifies PAC products. Although the formation of polynuclear aluminum species in solution has been studied for over a century, there is still much controversy concerning aluminum polymerization reactions and the resulting product compositions.

Commercially, PAC has been used in water (qv) and wastewater treatment in Japan, the USSR, and Europe since about 1970, and in the United States since the early 1980s (1). Aluminum chlorohydrate [12042-91-0], $\text{Al}_2\text{Cl}(\text{OH})_5$, a specialty PAC product, has been utilized as an antiperspirant for over 50 years (see COSMETICS) (2). Other PAC uses include preparation of pillared clay catalysts (3), stabilization of formation clays (see CLAYS) (4), paper (qv) sizing in papermaking (5), catalysts in durable-press finishing of fabrics (6), and preparation of alumina-coated silica sols (7).

Properties

Physical and chemical properties of the numerous PAC products can vary considerably. PAC products are usually aqueous solutions, although solid products are also sold. Solutions range from colorless to amber and from clear to hazy in appearance; specific gravities at 25 °C vary from about 1.2 to 1.35. Product viscosities, as measured by a Brookfield viscometer at 25 °C, are generally about 10–50 mPas (cP), but can be much greater than 10,000 mPas (cP) for certain aged compositions.

An empirical formula, $\text{Al}_n(\text{OH})_m\text{Cl}_{3n-m}$, where $0 < m < 3n$ can be written to describe overall PAC composition. The degree of neutralization of hydrated Al(III), or basicity, is expressed as the mole ratio of OH^-/Al (m/n). This ratio is often called the ligand or hydroxyl number r : aluminum chloride has $r = 0$; aluminum hydroxide, $r = 3$; and PAC products have r values ranging from about 0.5 to 2.5. PAC solution products are always acidic. The pH ranges from <1 to ca 4.0. The total aluminum concentration, conventionally expressed as Al_2O_3 or alumina content, is important to product composition and activity. Total Al content of PAC products as Al_2O_3 ranges from about 6 to 24% by weight in aqueous solutions. PAC products can also contain other inorganic salts, such as sodium, potassium, calcium, or magnesium chlorides and/or bromides, and these salts can affect PAC properties.

Whereas the nature of the Al species in PAC products is not fully understood, it appears that there are three or four species or molecular weight categories: monomers, a dimer, an Al_{13} polymer, and several higher Al polymers. ^{27}Al -nmr spectroscopy has been useful in the identification and quantification of these cations (8–14). Using an aluminum salt standard, the monomeric species hexaaquaaluminum ion [15453-67-5], $\text{Al}(\text{H}_2\text{O})^{3+}$, pentaquahydroxyaluminum (+2) ion [18499-02-0], $\text{Al}(\text{OH})(\text{H}_2\text{O})^{2+}_5$, and $\text{Al}(\text{OH})_2(\text{H}_2\text{O})^+_4$ exhibit a sharp peak at 0 ppm; the dimer, octaquadri-μ-hydroxydialuminum ion [46130-83-0] (Al_2), $\text{Al}_2(\text{OH})_2(\text{H}_2\text{O})^{4+}_8$, gives a broad, less readily discernible band at 3 ppm; and the polymeric species dodecaquatetracosia-μ-hydroxy-tetra-μ₄-oxotridecaaluminum ion [12703-68-3] (Al_{13}), $\text{Al}_{13}\text{O}_4(\text{OH})_{24}(\text{H}_2\text{O})^{7+}_{12}$, exhibits a sharp resonance indicating a tetrahedrally coordinated Al, such as in AlO_4 , at 62.5 ppm. The fraction of PAC products not identifiable by nmr may be polymeric and/or colloidal Al hydroxide precipitates (14). The distribution of Al species for two series of PACs was found to be a function of the ligand number r , as shown in Figure 1 (15).

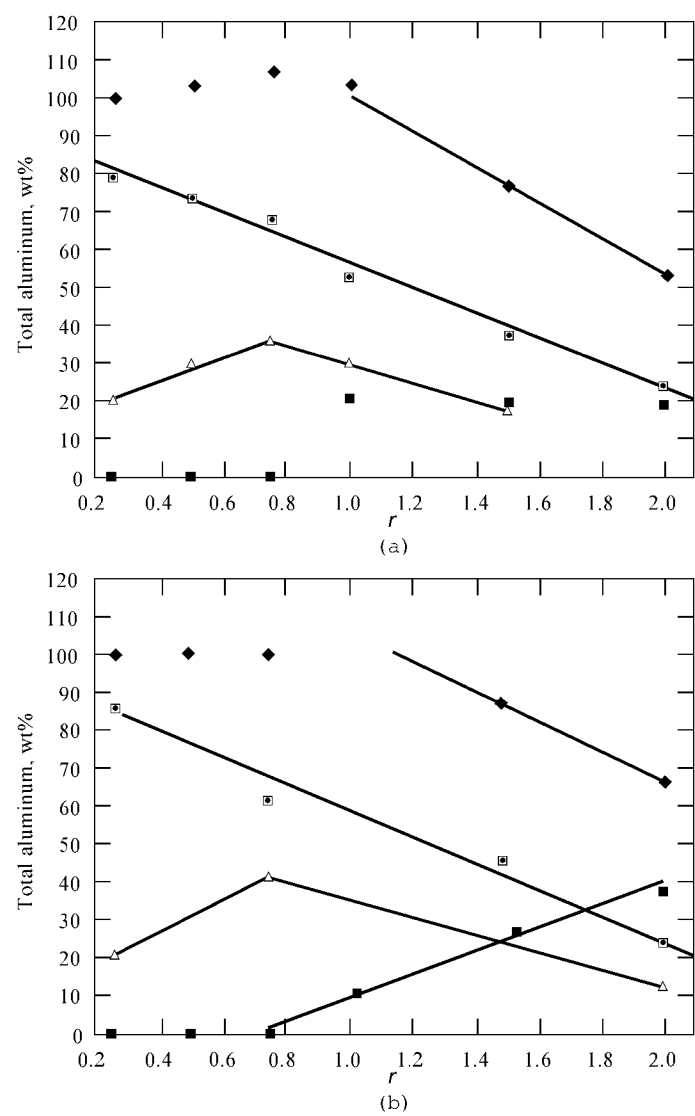


Fig. 1. Al species as a function of *r*, the OH /Al ratio. □, Monomers; Δ, dimer; ■, Al₁₃ polymer; ♦, the sum of the Al species for PACs prepared from 27° AlCl₃ (aq) and (a) Ca(OH)₂ and (b) Na₂CO₃.

The structure proposed for Al₁₃ is a central Al in a tetrahedral configuration having four oxygens surrounded by 12 AlO₄ octahedra (16). The existence of the tetrahedral Al has been explained by assuming that aluminate ion, AlO₄³⁻, is the Al₁₃ precursor. Whereas AlO₄³⁻ is not stable in solutions below pH 10, localized, high concentrations of hydroxide have been postulated to occur during aluminum chloride base neutralization, forming an aluminate ion (12). In processes utilizing Al metal, the oxidation of Al is accompanied by reduction of water to hydrogen gas creating a high hydroxide concentration on the metal surface (17). The resultant aluminate ion then rapidly reacts with octahedrally coordinated Al in the bulk solution, forming Al₁₃, which is sometimes written as an aluminate and a dodecamer, [AlO₄Al₁₂(OH)₂₄(H₂O)₁₂]⁷⁺.

The Al₁₃ polymer, readily recognizable and often predominant in PAC solutions, is probably the most stable, highly charged cation in PAC. Al₁₃ has an overall charge of +7 corresponding to a charge density of +0.54 /Al as compared to Al monomers with +3 charge and charge density. In applications where charge neutralization is an important mechanism for PAC activity, cations of highest charge may be most effective (18). Therefore, there is some indication that Al₁₃ content in PAC should be maximized (19). In a patented use of PAC chemistry in clarifying certain natural waters, however, it was found that maximizing the concentration of the dimer was most effective (15), even though Al₂ has an overall charge of +4 and a charge density of +2 /Al.

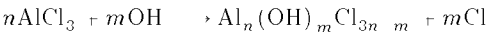
Aluminum Chlorohydrate

Aluminum chlorohydrate [12359-72-7], Al₂(OH)₅Cl·2H₂O is a PAC product of specific composition, having *r* = 2.5. Aluminum chlorohydrate is used in antiperspirants regulated by the U.S. Food and Drug Administration (FDA). Solutions sold for FDA-approved use are colorless in appearance, have 23–24° Al as Al₂O₃, and low levels of iron (<50 ppm), sulfate (<0.025 %), metals (Ca, Mg, Na <10 ppm), and heavy metals (as Pb <10 ppm). The pH of these solutions at 25°C is about 3.8–4.0. Typically, solutions at 25°C have specific gravities from 1.33 to 1.35 and viscosities from 40 to 60 mPas (cps). Aluminum chlorohydrate [12042-91-0] is also available in dry form with different particle-size distributions.

Characterization of aluminum chlorohydrate has revealed a predominance (about 88°) of Al₁₃ polymer with the balance being monomers and smaller polycations (20). The highly charged Al⁷⁺₁₃ surrounded by Cl⁻ counterions is self-stabilized by repulsion forces, preventing association and subsequent aluminum hydroxide precipitation (21). Thus, aluminum chlorohydrate solutions remain clear and free of precipitate after years of storage at room temperature. Aqueous dilution or an increase in pH to 5–6, however, results in rapid degradation and formation of gibbsite [14762-49-3], an insoluble aluminum hydroxide polymorph (8).

Manufacture

A generic manufacturing process for PAC involves the addition of base to aluminum chloride solution

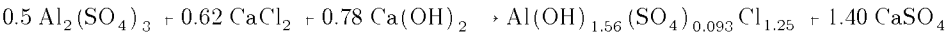


Typical values for *m/n* are 0.5 to 2.5. Commercially used bases include sodium hydroxide, potassium hydroxide, calcium hydroxide (lime), magnesium hydroxide, sodium carbonate, sodium aluminate, calcium carbonate, or various mixtures. For certain applications, PAC can be made from waste grades of aluminum chloride [7446-70-0] such as spent catalyst solutions from Friedel-Crafts synthesis (see FRIEDEL-CRAFT'S REACTION).

The OH /Al mole ratio or ligand number *r* is an important factor in the speciation of Al cations in the PAC product. Product composition also

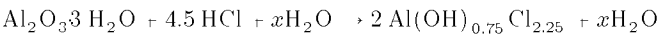
depends upon initial aluminum concentration, base addition rate, mixing intensity, and temperature (14). Al content of products from processes utilizing aluminum chloride as the Al source are less than 10⁰   as Al₂O₃ because the maximum solubility of aluminum chloride in water is about 30⁰   at 25 C.

Aluminum sulfate [7784-31-8] solutions can also be used for all or part of the PAC Al source. In one process, a mixture of alum and aluminum chloride is neutralized using calcium carbonate, and solid calcium sulfate [7778-18-9] is removed by filtration (22). In another process alum is mixed with calcium chloride and calcium hydroxide (23):



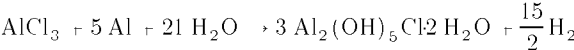
This PAC contains 1–2⁰   sulfate as soluble calcium sulfate. Sulfate has been found to make PAC products unstable: precipitate forms in less than one week at 50 C. Sulfate, however, has also been seen to increase PAC activity in water clarification and is thus intentionally added in one preparation (24). Precipitated calcium sulfate creates a sludge disposal problem. Typical Al content as Al₂O₃ of PAC products made from alum is 6–8⁰  .

Aluminum oxide solids can be utilized to manufacture PAC by the addition of acid (15). Alumina trihydrate [12252-70-9], Al₂O₃·3H₂O, a reactive intermediate from bauxite beneficiation, is first slurried with water, and the slurry is gradually added to concentrated hydrochloric acid. PAC forms when the HCl/Al₂O₃ mole ratio is less than 6; typical ratios in commercial processes are 3 to 4.5.



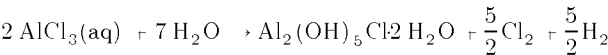
The reaction is facilitated by elevated temperature necessitating pressure-capable, glass-lined reactors and exotic metallurgy for fittings to withstand the severely corrosive conditions. PAC product having 10–12⁰   Al as Al₂O₃ can be produced.

Aluminum Chlorohydrate. A common process for the manufacture of aluminum chlorohydrate involves the addition of metallic Al to aluminum chloride



The reaction proceeds spontaneously, but can be accelerated by the use of an electrode more noble than Al, such as Fe, Sn, Ni, Pb, or graphite (25). Heavy metal salt catalysts, such as copper chloride and silver nitrate, have also been used to avoid heating (26). Hydrogen gas is generated by the reaction, so explosion hazards must be managed. Aluminum powder, turnings, cuttings, bars, and ingots have been used as the metal source. PAC product having 23–24⁰   Al as Al₂O₃ can be produced.

The electrolysis of aluminum chloride solutions may also be used to produce PAC having 23–24⁰   Al as Al₂O₃.



An electrolytic cell, preferably having anode and cathode compartments separated by a porous membrane to prevent formation of explosive gas mixtures, is required (27).

Shipping and Handling

Liquid polyaluminum chloride is acidic and corrosive to common metals. Suitable materials for construction of storage and handling facilities include synthetic rubber-lined steel, corrosion resistant fiber glass reinforced plastics (FRP), ceramics, tetrafluoroethylene polymer (PTFE), poly(vinylidene fluoride) (PVDF), polyethylene, polypropylene, and poly(vinyl chloride) (PVC). Suitable shipping containers include rubber-lined tank trucks and rail cars for bulk shipment and plastic-lined or all-plastic drums and tote bins for smaller quantities. Except for aluminum chlorohydrates, PAC products are shipped as hazardous substances because of their acidity.

Economic Aspects

Production figures for polyaluminum chlorides are not released by manufacturers. However, total U.S. production of PAC excluding aluminum chlorohydrate was estimated at 30,000 metric tons in 1989 from Nalco Chemical Company (Naperville, Ill.) and General Chemical Corporation (Parsippany, NY) and retail prices for polyaluminum chloride solutions were approximately \$0.30–\$0.70/kg. Three U.S. manufacturers of aluminum chlorohydrate, Reheis Chemical Company (Berkeley Heights, N.J.), Courtney Industries (Baltimore, Md.) and Westwood Chemical Corporation (Middletown, N.Y.) are estimated to produce 25,000 metric tons per year. There are other manufacturing companies that utilize all of their aluminum chlorohydrate internally in antiperspirant products; no estimate of this capacity can be made. The wholesale price of aluminum chlorohydrate in 1989 was about \$1.00/kg.

Specifications and Safety

Polyaluminum chloride products used in the treatment of potable (drinking) water must be approved by the National Sanitation Foundation (NSF). NSF certification has superseded EPA approval. Aluminum chlorohydrate for topical use as an antiperspirant is regulated by FDA.

Contact with polyaluminum chloride products may cause burns or irritation to the eyes or skin; thus, protective clothing and eye protections are recommended.

Uses

Water and Waste Water Treatment. PAC products are used in water treatment for removal of suspended solids (turbidity) and other contaminants such as natural organic matter from surface waters. Microorganisms and colloidal particles of silt and clay are stabilized by surface electrostatic charges preventing the particles from coalescing. Historically, alum (aluminum sulfate hydrate) was used to neutralize these charges by surface adsorption of Al cations formed upon hydrolysis of the alum. Since 1983 PAC has been sold as an alum replacement in the treatment of natural water for U.S. municipal and industrial use.

Alum and PAC usage have been compared (1,28,29), and PAC is advantageous in waters of low to moderate turbidity, possibly because of the greater charge-neutralizing capacity relative to alum (1). PAC, typically applied at much lower total Al dosages than alum, results in less aluminum hydroxide sludge to be dewatered (qv) and trucked out. Consumption of water alkalinity is significantly lower using PAC because of partial neutralization of Al, and savings are realized in treating low (less than 20 mg/L as CaCO₃) alkalinity waters when caustic, lime, or soda ash are conserved. Finally, the use of PAC in cold water treatment provides greater removal of turbidity than using alum because of the higher reactivity of PAC's preformed polymers at low temperatures (29). PAC products are similarly used in removal of suspended solids or dispersed oil (30) from waste waters, and for precipitation of fluoride and phosphates (31).

Antiperspirants. Aluminum chlorohydrate, widely used as an antiperspirant (32), came into usage in the early 1940s (2). The mechanism for antiperspirant activity is the formation of an obstructive aluminum hydroxide plug within the sweat gland duct (17). When aluminum chlorohydrate at body temperature is simultaneously diluted with sweat and exposed to the higher pH on the skin, insoluble aluminum hydroxide rapidly forms.

Preparation of Pillared Clay Catalysts. PAC products are used for the preparation of zeolite-like catalysts by intercalation, the insertion of Al polycations molecules between the aluminosilicate sheets of clay (3,33). Aqueous clay suspensions are slowly added to vigorously stirred PAC solutions, and the reaction mixture is aged for several hours. The clay is separated from the PAC solution and washed free of chloride ion. The treated clay is first dried at low temperature and then calcined in air at 450–500 C, producing a high surface area material having a regular-sized pore opening of about 0.6 to

1.0 nm. These pores openings are shape selective for molecules, allowing pillared clays to be used for hydrocarbon cracking. Selectivities are similar to zeolitic catalysts (see MOLECULAR SIEVES) (33).

Catalysts for Finishing of Durapress Fabrics. PAC products are used as catalysts in the textile finishing industry (see TEXTILES) (6,34). Fabric is impregnated with a finishing agent such as dimethylol methyl carbamate and a catalyst in aqueous solution, dried, and heat cured. Whereas various types of aluminum salts can be used as catalysts, PAC is preferred because PAC use avoids fabric degradation and discoloration.

Papermaking Use. PAC is widely used in Europe in papermaking processes. The gradual changeover from acid to alkaline systems in U.S. paper mills is expected to be accompanied by an increase in the use of PAC as an alum replacement (35).

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AMALGAMATION PROCESS.

See GOLD AND GOLD COMPOUNDS; MERCURY.

AMALGAMS.

See MERCURY.

AMATOL.

See EXPLOSIVES.

AMBER.

See RESINS, NATURAL.

AMBERGRIS.

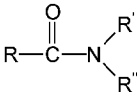
See PERFUMES.

AMERICIUM.

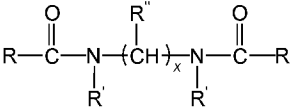
See ACTINIDES AND TRANSACTINIDES.

AMIDES, FATTY ACID

Fatty acid amides are of the general formula



in which R may be a saturated or unsaturated alkyl chain derived from a fatty acid. They can be divided into three categories (1). The first is primary monoamides in which R is a fatty alkyl or alkenyl chain of C₅–C₂₃ and R' = R'' = H. The second is substituted monoamides , including secondary, tertiary, and alkanolamides in which R is a fatty alkyl or alkenyl chain of C₅–C₂₃; R' and R'' may be a hydrogen, fatty alkyl, aryl, or alkylene oxide condensation groups with at least one alkyl, aryl, or alkylene oxide group. The third category is bisamides of the general formula:



where R groups are fatty alkyl or alkenyl chains. R' and R'' may be hydrogen, fatty alkyl, aryl, or alkylene oxide condensation groups. Other amides include halogenated amides and multifunctional amides such as amidoamines and polyamides. A more detailed description of the synthesis, properties, and reactions of amides can be found in reference 2. Examples of fatty acid amides and common nomenclature for primary amides can be seen in Table 1.

Table 1. Primary Fatty Amide (RCONH₂) Nomenclature

Carbon atoms ^a	Common name	Molecular formula	IUPAC name	CAS Registry Number
12	lauramide	C ₁₂ H ₂₅ NO	<i>Alkyl</i> dodecylamide	[1120-16-7]
14	myristamide	C ₁₄ H ₂₉ NO	tetradecylamide	[638-58-54]
16	palmitamide	C ₁ H ₃₃ NO	hexadecylamide	[629-54-9]
18	stearamide	C ₁₈ H ₃₇ NO	octadecylamide	[124-26-5]
			<i>Alkenyl</i>	

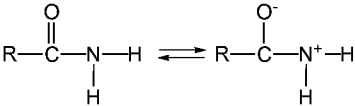
16(1)	palmitoleamide	C ₁ H ₃₁ NO	hexadecenamide	^b
18(1)	oleamide	C ₁₈ H ₃₅ NO	9-octadecenamide	[301-02-0]
18(2)	linoleamide	C ₁₈ H ₃₃ NO	9,12-octadecadienamide	[3999-01-7]

^a The number in parentheses designates double bonds in the carbon chain.

^b Not available.

Physical Properties

Many of the physical properties of fatty acid amides have been explained on the basis of the tautomeric structures:



Primary and secondary amides show strong hydrogen bonding which accounts for their high melting points and low solubilities in most solvents. With tertiary amides (disubstituted amides), hydrogen bonding is not possible as exhibited by their increased solubility and lower melting points as shown in Table 2 (3). Many fatty acid amides are essentially insoluble in water. Polar solvent solubilities decrease with longer alkyl chain lengths. Amides with alkyl lengths more than C₁₂, with the exception of alkanolamides, have low solubility in all solvents. In nonpolar solvents, solubility is low and varies irregularly with chain length (4).

Table 2. Fatty Amide Melting Points

Alkyl(R) length	RCONH ₂ Amide		RCONHCH ₂ CH ₂ OH		RCON(CH ₂ CH ₂ OH) ₂	
	CAS Registry Number	Mp, °C	Monoethanolamide		Diethanolamide	
			CAS Registry Number	Mp, °C	CAS Registry Number	Mp, °C
12	[1120-16-7]	103	[142-78-9]	78.2	[120-40-1]	38.7
14	[638-58-4]	104	[142-58-5]	87.4	[7545-23-5]	47.9
16	[629-54-9]	108	[544-31-0]	94.4	[7545-24-6]	65.1
18	[124-26-5]	109	[111-57-9]	96.1	[93-82-3]	69.7

Amides have a strong tendency to reduce friction on various surfaces by forming a layer on surfaces. This coating action may be attributed to their hydrophobic character and strong hydrogen bonding. Amides are widely used as lubricating or slip agents. Detailed descriptions of their properties can be found in the literature (5–7).

Chemical Properties

Amides in general are stable to elevated processing temperatures, air oxidation, and dilute acids and bases. Stability is reduced in amides containing unsaturated alkyl chains; unsaturation offers reactive sites for many reactions.

Hydrolysis of primary amides catalyzed by acids or bases is very slow. Even more difficult is the hydrolysis of substituted amides. The dehydration of amides which produces nitriles is of great commercial value (8). Amides can also be reduced to primary and secondary amines using copper chromite catalyst (9) or metallic hydrides (10). The generally unreactive nature of amides makes them attractive for many applications where harsh conditions exist, such as high temperature, pressure, and physical shear.

Synthesis and Manufacture

Unsubstituted Amides. The most widely used synthetic route for primary amides is the reaction of fatty acid with anhydrous ammonia (11). Fatty acid and ammonia are allowed to react at approximately 200°C for 10 to 12 h under a constant vent of excess ammonia and water by-product. A pressure of 345–690 kPa (50–100 psi) is maintained by the addition of ammonia while the venting of water facilitates the completion of the reaction.



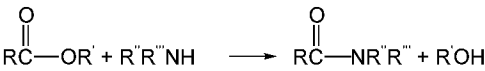
Lauramide has been prepared by passing ammonia gas through lauric acid in the presence of metallic oxides, specifically a complex mixture of SiO₂–Al₂O₃–Fe₂O₃–CaO–SO₃ in the ratio of 24:16:3:47:10. The oxides, which are hydrated during amidation, can be regenerated by calcination (12,13).

A continuous process has been described (14) which can produce either the amide or the nitrile by adjusting the reaction conditions. Boric acid has been used as a catalyst in the amidation of fatty acid (15). Other catalysts employed include alumina (16), titanium, and zinc alkoxides (17). The difficulty of complete reaction during synthesis has been explained by the formation of RCOOH·NH₄⁺ RCOO[–], a stable intermediate acid ammonium salt (18).

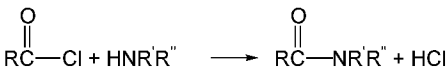
Amide yields of up to 90–95% are reported from lauric acid and urea (1:1 mole ratio) by ramping the reaction temperature from 140 to 190°C over 4 hours. Oleic, stearic, linoleic, and ricinoleic acids gave similar results (19,20). The reaction does not form significant quantities of bisamides, but relies on the decomposition of a substituted urea amide, releasing CO₂ and NH₃.



Amides can be produced from fatty acid methyl esters by reaction with ammonia at 220 °C at 12.4 MPa (1800 psi) pressure. Reaction times are reduced to 1 h by this route; however, the fatty acid feedstocks must first be converted to methyl esters (21).



The hydrogenolysis of hydroxamic acids (22) and hydrazides (23) has also been used to synthesize amides. One of the earliest methods for the preparation of amides consists of treating acid chlorides with dry ammonia or an amine (24).

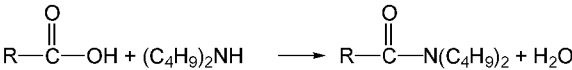


The hydration of nitriles has been used to synthesize amides, for example, by treating stearonitrile in ether with dry hydrochloric acid followed by the addition of water to give a 73–94% yield of stearamide or its hydrochloride (25). The long reaction time at 0°C and the use of ether make this route of little commercial value.

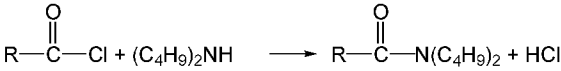
The ability of lipases to synthesize the amide bond has been shown (26). *Mucor miehei* lipase (NOVO lipozyme) has been used in the reaction of laurylamine and oleic acid at 60°C. Water was shown to inhibit the synthesis of this *N*-lauryloleamide (27).

N-Chloro fatty acid amides have been synthesized from the direct halogenation of the amide in boiling water (28). They are useful as reactive intermediates for further synthesis. Fluorination has also been reported by treating the fatty amide with fluorine-containing acid reagents at 200 °C to reach a fluorinated amide with less reactivity toward fluorocarbon polymers (29).

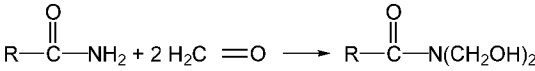
Substituted Amides. Monosubstituted and disubstituted amides can be synthesized with or without solvents from fatty acids and alkylamines. Fatty acids, their esters, and acid halides can be converted to substituted amides by reaction with primary or secondary alkylamines, arylamines, polyamines, or hydroxyalkylamines (30). Di-*n*-butylamine reacts with oleic acid (2:1 mole ratio) at 200–230°C and 1380 kPa (200 psi) to produce di-*N*-butyloleamide. Entrained water with excess *n*-butylamine is separated for recycling later (31).



Refluxing linoleic acid and a primary or secondary alkyl amine with *p*-toluenesulfonic acid in toluene for 8–18 h also yields the substituted amides (32–34). The reaction of methyl esters with primary or secondary amines to make substituted amides is catalyzed with sodium methoxide. Reactions are rapid at 30°C under anhydrous conditions (35). Acid chlorides can also be used. *N,N*-dibutyloleamide [5831-80-1] has been prepared from oleoyl chloride and dibutyl amine (36).



Alkanolamides, a special subclass of substituted amides used as surfactants, are produced by three principal methods: the reaction of fatty amides with formaldehyde, fatty acids with hydroxyalkylamines, and fatty esters with hydroxyalkylamines (37). A fatty amide and formalin can be heated in the presence of sodium hydroxide to yield 70–95% substituted alkanolamides (38,39).



Reactions of fatty acids and hydroxyalkylamines yield low purity products which are water soluble (40). They are prepared at 160–180°C while venting the water produced with 85–95% yields. Higher purity can be obtained by the reaction of fatty acid esters with hydroxyalkylamines in the presence of alkali (41) or alkali metal oxides (42,43). These "superamides" are water insoluble and have better foam stability and rheological characteristics in aqueous dispersions. Disubstituted alkanolamides can be synthesized from many mono or dialkylene oxide amine condensation products. More complex but commercially useful Lamepon, RCON(CH₃)CH₂COONa (44), and Igepon, RCON(CH₃)CH₂CH₂SO₃Na (45) amides can be prepared from acylation with fatty acid chlorides.

Another subclass of substituted amides that is of great commercial value is the ethoxylated amides. They can be synthesized from alkanolamides by chain extending with ethylene or propylene oxide or by ethoxylation directly from the primary amide (46–48). It was originally believed that the stepwise addition of ethylene oxide (EO) would produce the monoethanolamide and then the diethanolamide when sufficient ethylene oxide was added (49), but it has been discovered that only one hydrogen of the amide is substituted with ethylene oxide (50–53). As is typical of most ethylene oxide adducts, a wide distribution of polyethylene oxide chain length is seen as more EO is added. A catalyst is necessary to add ethylene oxide or propylene oxide to a primary or an ethoxylated amide or to ethoxylate a diethoxy alkanolamide synthesized from diethanolamine (54).

Bisamides. Methylenebisamides are prepared by the reaction of the primary fatty amide and formaldehyde in the presence of an acid catalyst. *N,N'*-Methylenebisoleamide has been made via this route without the use of refluxing solvent (55). Polymethylenebisamides can be made from fatty acid, esters, or acid halides with diamines while producing water, alcohol, or mineral acid by-products. Fatty acids and diamines, typically ethylenediamine, have been condensed in the presence of NaBH₄ and NaH₂PO₂ to yield bisamides (56). When stearic acid, ethylenediamine, and methyl acetate react for 6 h at 180°C under nitrogen, the yield is 56% *N,N'*-ethylenebissearamide [110-30-5] (57). Other polyamides can be prepared from polyamines in a similar fashion.

Commercial Aspects

Many primary fatty amides which are available from various manufacturers are listed in Table 3. In 1986 approximately 55,000 metric tons of amides and bisamides were produced world wide (58), the majority of which are bisamides, followed in volume by primary amides. Most of these products are shipped in solid form in bag or drum quantities. Major producers of primary fatty amides are Akzo, Glyco, Humko, and Sherex. Bisamides are produced by Akzo, Milacron, and Syntex. There are over 100 producers of alkanolamides in the world, most of which are small specialized manufacturers to a specific industry. GAF, Henkel, Sherex, and Witco are among the principal producers. The most widely used alkanolamides are the *N,N*-bis(2-hydroxyethyl) fatty amides, mostly produced from middle-cut coco fatty acids (6% caprylic, 7% capric, 51% lauric, 19% myristic, 9% palmitic, and 2% stearic acids). An estimated 77,000 metric tons of alkanolamide was produced worldwide in 1986 (59).

Table 3. Primary Fatty Acid Amides

Common name	CAS Registry Number	Trade name	Manufacturer	Physical form	Price ^a , \$ /kg
coco fatty amide	[61789-19-3]	Armid C	Akzo	solid, flake	3.48
stearamide	[124-26-5]	Adogen 60	Sherex	solid	3.00
		Armid 18	Akzo	flake	
		Kemamide S	Humko	beads	
		Adogen 42	Sherex	beads	
hydrogenated-tallow fatty amide	[61790-31-6]	Armid HT	Akzo	flake, powder	2.84
		Adogen 40	Sherex	beads	
docosanamide	[3061-75-4]	Adogen I	Sherex	beads	

octadecenamide	[112-90-3]	Kemamide B	Humko	powder	2.89
		Adogen 72	Sherex	solid, flake	
		Armid O	Akzo	solid, flake	
		Armoslip CP	Akzo	pellet, flake	
13-docosenamide	[112-84-5]	Kemamide U	Humko	powder	5.64
		Kemamide E	Humko	powder, flake	
		Armid E	Akzo	flake, pellet	
		Armoslip E	Akzo	pellet, powder	

^a Approximate, 1990.

Table 4 lists many of the commercially available substituted fatty acid amides. The *N,N*-dimethylamides, ethoxylated amides, and other specialty substituted amides are available in commercial quantities, but are of lower volume.

Table 4. Substituted Fatty Acid Amides

Chemical identity	CAS Registry Number	Trade name	Manufacturer	Form
<i>N,N</i> -bis(2-hydroxyethyl) dodecanamide	[120-40-1]	Ninol AA62 Extra	Stepan	wax
<i>N,N</i> -bis(2-hydroxyethyl)coco fatty acid amide	[68603-42-9]	Ninol 2021 Extra	Stepan	flakes
<i>N</i> -(2-hydroxypropyl)-dodecanamide	[142-54-1]	Ninol AD31	Stepan	flakes
octadecenylpeptide, sodium salt		Maypon K	Maywood	44° o soln.
<i>N</i> -methyl- <i>N</i> -(1-oxododecyl)-glycine	[97-78-9]	Sarkosyl L	CIBA GEIGY	95° o powder
<i>N</i> -methyl- <i>N</i> -(1-oxooctadecyl)-glycine	[142-48-3]	Sarkosyl S	CIBA GEIGY	powder
<i>N</i> -methyl- <i>N</i> -(1-oxooctadecenyl)-glycine	[110-25-8]	Sarkosyl O	CIBA GEIGY	paste
<i>N,N</i> -dimethylhexanamide	[5830-30-8]	Hallcomid M6	Hall	liquid
<i>N,N</i> -dimethyldodecanamide	[3007-53-2]	Hallcomid M12	Hall	liquid
<i>N,N</i> -dimethyloctadecanamide	[3886-90-6]	Hallcomid M18	Hall	solid
<i>N,N</i> -dimethyloctadecenamide	[2664-42-8]	Hallcomid M18-OL	Hall	liquid
1,2-ethanediylbis-octadecanamide	[110-30-5]	Acrawax C	Glyco	powder beads
		Kemamide W40	Humko	powder
		Armowax	Akzo	powder
1,2-ethanediylbis-octadecenamide	[110-31-6]	Kemamide W20	Humko	powder
<i>Sodium N-acyl-N-methylaminoethanesulfonates</i>				
from coco fatty acid	[12765-39-8]	Igepon TC-42	GAF	22° o soln.
from tallow fatty acid	[39387-16-1]	Igepon TE-42	GAF	24° o soln.
from octadecenoic acid	[137-20-2]	Igepon T-77	GAF	67° o flake
from hexadecanoic acid	[3737-55-1]	Igepon TN-71	GAF	14.5° o soln.

Analysis

Amides can be titrated directly by perchloric acid in a nonaqueous solvent (60,61) and by potentiometric titration (62), which gives the sum of amide and amine salts. Infrared spectroscopy has been used to characterize fatty acid amides (63). Mass spectroscopy has been able to indicate the position of the unsaturation in unsaturated fatty amides (64). Typical specifications of some primary fatty acid amides and properties of bisamides are shown in Tables 5 and 6.

Table 5. Amide Specifications^a

Primary amide	CAS Registry Number	Iodine number ^b	Fatty acid, max ^o o	Mp, °C	Gardner color ^b
coco fatty amide	[61789-19-3]	10	4.0	85 min	10
hydrogenated tallow amide	[61790-31-6]	5	5.0	98–103	7
stearamide	[124-26-5]	95 ^c	3.5	68 min	7
oleamide	[361-02-0]	2	5.0	99–109	7

^a Amide, 90° o minimum.

^b Maximum.

^c Minimum 80.

Table 6. Substituted Amide Properties

Substituted amides	CAS Registry Number	Molecular formula	Melting range, °C	Flash point ^a , °C	Gardner color
ethylenebis-stearamide (EBS)	[110-30-5]	C ₃₈ H ₇ N ₂ O ₂	140–145	304	3
methylenebis-stearamide (MBS)	[109-23-9]	C ₃₇ H ₇₄ N ₂ O ₂	135–140	260	5
oleyl stearamide	^b	C ₃ H ₇₁ NO	70–75	260	3
stearyl stearamide	[13276-08-9]	C ₃ H ₇₃ NO	92–95	246	4

^a Tag closed cup.

^b Not available.

Uses

Primary amides and bisamides are used primarily for their lubricity and surface active nature because of their inherent hydrogen bonding, insolubility, incompatibility, and unreactivity. They form very thin layers on the surfaces of polymers providing slip and blocking resistance. The long fatty chain is believed to penetrate the polymer matrix and the polar nature of the amide functionality causes it to orient above the surface of the resin to provide this lubricity (65). Primary fatty acid amides are used in low density polyethylene (LDPE), polypropylene, and linear low density polyethylene (LLDPE) polymers especially in films, incorporated at 0.05–0.4%. The lubrication allows the film surfaces to slip freely past one another and prevents them from sticking together when wound under high tension. They have also been used in polyolefins, vinyl polymers, acrylic polymers, and polystyrene as antiblock additives. Erucamide [112-84-5], CH₃(CH₂)₇CH=CH(CH₂)₁₁CONH₂, is the most commonly used slip agent in the United States for this application.

Primary amides are also used as intermediates in the production of water repellents for textiles of the Zelan or Velan type. Primary amide, formaldehyde, pyridine, and hydrochloric acid are used to form water soluble quaternary salts, which are applied to the fabric and heated to form a water repellent treatment. They are frequently used as mold release agents (qv), by spraying onto molds for injection molding or by compounding in rubber before curing. Primary amides are added to lubricating oils to reduce friction and wear. They are added to a wide variety of coatings to reduce friction, trap pigments, repel water, and to provide other surface active or catalytic properties (66). The surface activity of primary amides inhibits corrosion in oils and increases the efficiency of color pigments for inks (qv).

Substituted amides (not of the alkanolamide variety) are sold to diverse low volume markets. They have some utility in polymers such as polyethylene, ethylene-vinyl acetate copolymers, acrylic polymers, PVC, polyamides, and polyesters. They have been found effective as pharmaceutical processing aids, defoamers (qv), antimicrobials, pesticides, insect repellents, dispersion stabilizers, and corrosion inhibitors.

Alkanolamides provide excellent increase in the detergency properties of formulations containing other surfactants. The addition of 5% superamide with 20% anionic surfactant and 75% of detergent builder and salt filler can increase detergency by one-third. They are foam boosters and are added to soap bars to facilitate lime soap dispersion, intensify the perfume, increase cracking tendency, and inhibit rancidity. They have served as detergent additives in janitorial and industrial cleaning preparations. Alkanolamides are used as thickening agents in liquid detergents or adjuvants to other nonassociative thickeners (67). They are also used as general emulsifying and wetting agents; as demulsifying agents for breaking water in oil emulsions; as germicides; and as plasticizers (qv) in certain resins. The largest consumption is in personal care products, such as shampoos and toothpaste. Longer chain alkylene oxide adducts are used in soap bars, liquid detergents, abrasive liquid cleaners, bleaching mixtures, and as detergents for wool and cotton cloths. They have also been employed in mineral oil and petroleum fraction formulations to reduce corrosion. Their increased dispersibility has allowed their use as acid pickling inhibitors.

The more complex Lamepon and Igepon type of amides, including the sarcosine (*N*-methylglycine) [107-97-1] and *N*-methyl taurine (*N*-methyamino-ethanesulfonate) types shown in Table 4, are used primarily as specialty surfactants in shampoo and toothpaste formulations. These rather complex structures have limited use in very specialized applications.

Fatty bisamides are used primarily to increase slip, reduce blocking, and reduce static in polymeric systems. Other specialty applications include cosolvents or coupling agents for polyamide resins, fillers for electrical insulation coatings, additives for asphalt to reduce cold flow, and synthetic waxes for textile treatments (68). Bisamides have been used in all the traditional primary amide applications to increase lubricity and have become the amide of choice because of their better efficiency. Bisamides have the highest commercial value in the amide market.

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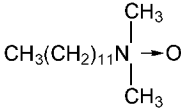
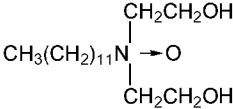
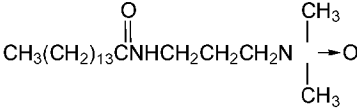
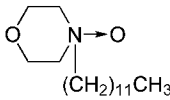
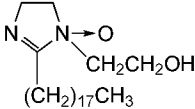
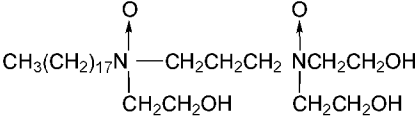
Ross Opsahl
Akzo Chemicals Corporation

AMINE OXIDES

Amine oxides, known as *N*-oxides of tertiary amines, are classified as aromatic or aliphatic, depending on whether the nitrogen is part of an aromatic ring system or not. This structural difference accounts for the difference in chemical and physical properties between the two types.

The higher aliphatic amine oxides are commercially important because of their surfactant properties and are used extensively in detergents. Amine oxides that have surface-acting properties can be further categorized as nonionic surfactants; however, because under acidic conditions they become protonated and show cationic properties, they have also been called cationic surfactants. Typical commercial amine oxides include the types shown in Table 1.

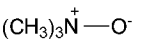
Table 1. Commercial Amine Oxides

Name	Molecular formula	CAS Registry Number	Structural formula
dimethyldodecyl-amine oxide	C ₁₄ H ₃₁ NO	[1643-20-5]	
dihydroxyethyl-do-decylamine oxide	C ₁ H ₃₅ NO ₃	[2530-44-1]	
dimethyltetradecyl-amidopropyl amine oxide	C ₂₀ H ₄₀ NO ₂		
<i>N</i> -dodecylmorpholine <i>N</i> -oxide	C ₁ H ₃₃ NO ₂	[2530-46-3]	
1-hydroxyethyl-2-octa-decyl imidazoline oxide	C ₂₃ H ₄ N ₂ O ₂		
<i>N,N',N'</i> -hydroxyethyl- <i>N</i> -octadecyl-1, 3-propylene-diamine oxide	C ₂₇ H ₅₈ N ₂ O ₅		

Aromatic amine oxides, produced on a much smaller scale and having some pharmaceutical importance, do not demonstrate the surface-acting properties that the aliphatic amine oxides do.

Physical Properties

The physical properties of amine oxides are attributed to the semipolar or coordinate bond between the oxygen and nitrogen atoms with high electron density residing on oxygen.



The N—O bond distances, found to be 0.133 to 0.139 nm for trimethylamine oxide (1), are somewhat shorter than the single N—C bond distance of 0.147 nm in methylamine. The N—C bond distance of 0.154 nm in trimethylamine oxide approaches that of the C—C bond. This is in agreement with the respective absorptions in the infrared region; valence vibrations of N—O bonds of aliphatic amine oxides are found between 970–920 cm^{−1} (2).

A dipole moment of 1.46 × 10^{−29} C·m (4.38 D) for the nitrogen-oxygen bond is larger than the moments of other semipolar bonds (3). The spatial arrangement around nitrogen in amine oxides is tetrahedral as in quaternary ammonium salts. Tetrahedral configuration was demonstrated by Meisenheimer, who separated *N*-ethyl-*N*-methylaniline *N*-oxide [825-19-4] into its optical isomers (4), and later confirmed by electron diffraction studies (1).

For the aromatic amine oxides, the trigonal nitrogen forces the oxygen into the same plane as the aromatic ring and permits resonance structures involving the nonbonded electrons on oxygen. This is largely responsible for the distinction between aliphatic and aromatic amine oxides and accounts for the added stability and special properties of aromatic amine oxides. Although amine oxides are weaker bases than the amines from which they are derived,

there is a base leveling effect in the oxides that is not found in the amines. This leveling effect is probably caused by the decreased effect of substituents which are further removed from the basic oxygen center (Table 2). Aromatic amine oxides are generally weaker bases than aliphatic amine oxides. However there are exceptions, eg, 1,10-phenanthroline monoxide [1891-19-6] is a stronger base than most aliphatic amine oxides because of stabilization of the conjugate acid through intramolecular hydrogen bonding (5).

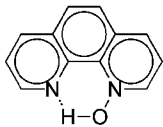


Table 2. pK_a Values of Protonated Amines and Their *N*-Oxides

Parent amine	Amine Registry Number	pK_a amine	Oxide molecular formula	Oxide Registry Number	pK_a <i>N</i> -oxide
(CH ₃) ₃ N	[75-50-3]	9.74	C ₃ H ₉ NO	[1184-78-7]	4.65
(C ₂ H ₅) ₃ N	[121-44-8]	10.76	C ₆ H ₁₅ NO	[2687-45-8]	5.13
C ₆ H ₅ N(CH ₃) ₂	[121-69-7]	5.06	C ₈ H ₁₁ NO	[874-52-2]	4.21
C ₆ H ₅ N(C ₂ H ₅) ₂	[91-66-7]	6.56	C ₁₀ H ₁₅ NO	[826-42-6]	4.53
<i>o</i> -CH ₃ C ₆ H ₄ N(CH ₃) ₂	[609-72-3]	5.86	C ₉ H ₁₃ NO	[6852-47-7]	4.78
<i>p</i> -CH ₃ C ₆ H ₄ N(CH ₃) ₂	[99-97-8]	5.50	C ₉ H ₁₃ NO	[825-85-4]	4.32

Amine oxides show either nonionic or cationic behavior in aqueous solution depending on pH. In acid solution the cationic form (R₃N⁺OH) is observed (2) while in neutral and alkaline solution the nonionic form predominates as the hydrate R₃NO·H₂O. The formation of an ionic species in the acidic pH range stabilizes the form generated by the most studied commercial amine oxide, dimethyldodecylamine oxide (6). Aliphatic amine oxides behave as typical surfactants in aqueous solutions. Below the critical micelle concentration (CMC), dimethyldodecylamine oxide exists as single molecules. Above this concentration micellar (spherical) aggregates predominate in solution. Aliphatic amine oxides are similar to other typical nonionic surfactants in that their CMC decreases with increasing temperature.

Temperature, °C	CMC, mol/L
1	0.0028
27	0.0021
40	0.0018
50	0.0017

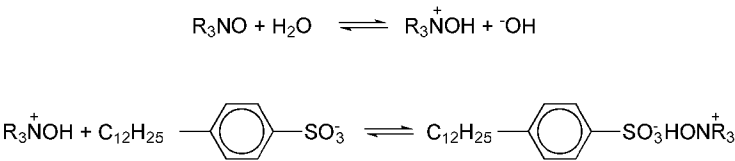
Wetting times of *N,N*-dimethyl-*n*-alkylamine oxides as a function of the alkyl chain length show a minimum with dimethyldodecylamine oxide (Table 3). Foam generation of dimethyl-*n*-alkylamine oxides solutions show a maximum when the alkyl group contains 14 carbons.

Table 3. Surfactant Properties of *N,N*-Dimethylalkylamine Oxides

Amine oxide	CAS Registry Number	Alkyl chain length	Wetting time, s	Foam height ^a , mm
dimethyloctylamine oxide	[2605-78-9]	8	900	
dimethyldecylamine oxide	[2605-79-0]	10	150	138
dimethyldodecylamine oxide	[1643-20-5]	12	37	175
dimethyltetradecylamine oxide	[3332-27-2]	14	225	185
dimethylhexadecylamine oxide	[7128-91-8]	16	900	30
dimethyloctadecylamine oxide	[2571-88-2]	18		17

^a Concentration = 3 g/L at 20°C.

In the presence of an anionic surfactant such as sodium dodecyl-benzenesulfonate [25155-30-0] any protonated amine salt present forms an insoluble salt (4). Salt formation results in an increase in the pH of the solution.

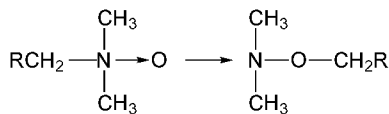


The effect of added inorganic salts on the micellar properties of the nonionic and cationic forms of dimethyldodecylamine oxide has been determined (2). Aliphatic amine oxides form charge-transfer complexes with iodine (7) because of the asymmetric electron distribution in the N–O bond with oxygen being the electron donor. Complexes of aliphatic amine oxides are stronger than those of aromatic ones (8). Amine oxides form hydrogen bonds with strong acids (9) and weak acids such as phenols (10). Trimethylamine oxide dihydrate contains strongly bound tricoordinated water and the hydrate water forms with the oxygen of the amine oxide is a structure similar to the water–fluoride cluster in tetraethylammonium fluoride dihydrate [63123-01-3] (11). Aliphatic amine oxides form complexes with metals or metallic salts (12).

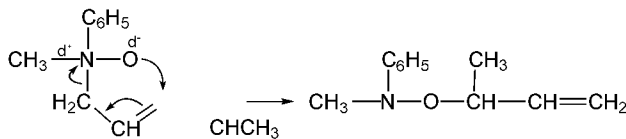
Reactions

Decomposition. Most amine oxides undergo thermal decomposition between 90 and 200 °C. Aromatic amine oxides generally decompose at higher temperatures than aliphatic amine oxides and yield the parent amine.

Rearrangement. Aliphatic amine oxides without an aliphatic hydrogen atom β to the nitrogen undergo Meisenheimer's rearrangement when heated to give trisubstituted hydroxylamines.

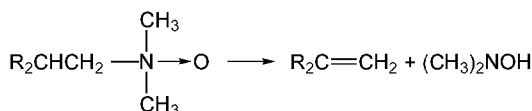


Allyl or benzyl groups on the nitrogen facilitate the process. The rearrangement appears to be intramolecular (13), proceeding by a cyclic mechanism as in the case of *N*-2-butenyl-*N*-methylaniline oxide giving *N*-methyl-*O*-1-methylallyl-*N*-phenyl-hydroxylamine.

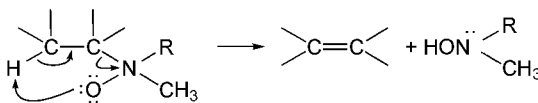


The rate of rearrangement increases as the basicity of the parent tertiary amine decreases (14). Strong support for a free-radical mechanism has been demonstrated (15,16).

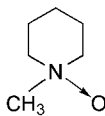
Elimination. Aliphatic amine oxides having an aliphatic hydrogen β to the nitrogen form olefins and dialkyl hydroxylamines when heated. This reaction is known as the Cope elimination (17)



and proceeds through a planar five-center intermolecular mechanism (18,19):

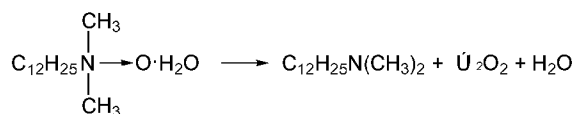


N-methylpiperidine oxide [17206-00-7] does not undergo the reaction because of its inability to achieve the highly strained transition configuration, whereas the

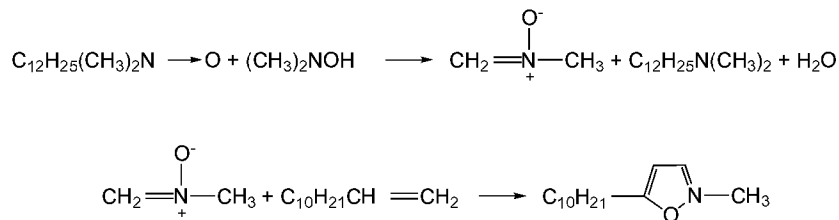


corresponding seven- and eight-membered ring compounds yield respectively 57% and 78% of the elimination product (18). When more than one possibility for elimination exists, it occurs predominantly toward the alkyl group having the most β -hydrogens, or one having an electron withdrawing group attached to the β -carbon (20). Stereoselectivity for this elimination reaction is predominantly *cis* (21) and allows for the preparation of certain olefins that could not otherwise be made using other elimination reactions that follow either the Hoffmann rule or the Saytzeff rule (19).

In the pyrolysis of pure amine oxides, temperature has a significant effect on the ratio of products obtained (22). The principal reaction during thermal decomposition of *N,N*-dimethyl-laurylamine oxide [1643-20-5] at 80–100°C is deoxygenation to *N,N*-dimethyl-laurylamine [112-18-5] (lauryl – dodecyl).



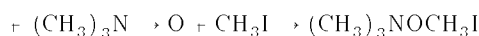
However, when the temperature is increased to 120°C, the principal reaction is the elimination to olefin. The thermal decomposition of dimethyldodecylamine oxide at 125°C in a sealed system, as opposed to a vacuum used by Cope and others, produces 2-methyl-5-decylisoxazolidine, dimethyldodecylamine, and olefin (23). The amine oxide oxidizes *N,N*-dialkylhydroxylamine to the nitron during the pyrolysis and is reduced to a tertiary amine in the process.



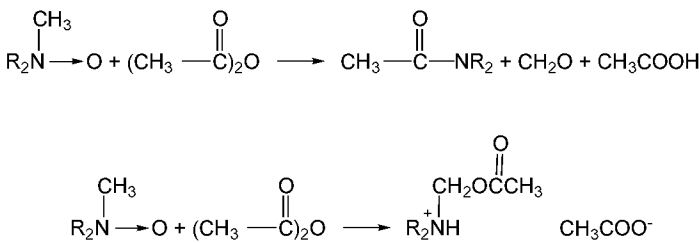
Metal Catalysis. Aqueous solutions of amine oxides are unstable in the presence of mild steel and thermal decomposition to secondary amines and aldehydes under acidic conditions occurs (24,25). The reaction proceeds by a free-radical mechanism (26). The decomposition is also catalyzed by V(III) and Cu(I).

Reduction. Just as aromatic amine oxides are resistant to the foregoing decomposition reactions, they are more resistant than aliphatic amine oxides to reduction. Aliphatic amine oxides are readily reduced to tertiary amines by sulfurous acid at room temperature; in contrast, few aromatic amine oxides can be reduced under these conditions. The aliphatic amine oxides can also be reduced by catalytic hydrogenation (27), with zinc in acid, or with stannous chloride (28). For the aromatic amine oxides, catalytic hydrogenation with Raney nickel is a fairly general means of deoxygenation (29). Iron in acetic acid (30), phosphorus trichloride (31), and titanium trichloride (32) are also widely used systems for deoxygenation of aromatic amine oxides.

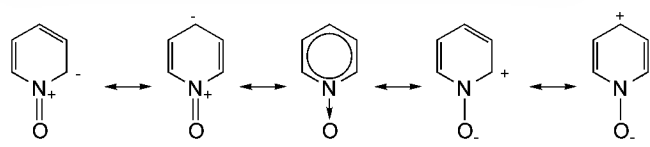
Alkylation. Alkylating agents such as dialkyl sulfates and alkyl halides react with aliphatic amine oxides to form trialkylalkoxyammonium quaternaries. For example (33), methyl iodide reacts with trimethylamine oxide to form trimethylmethoxyammonium iodide



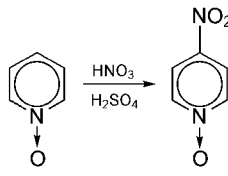
Acylation. Aliphatic amine oxides react with acylating agents such as acetic anhydride and acetyl chloride to form either *N,N*-dialkylamides and aldehyde (34), the Polonovski reaction, or an ester, depending upon the polarity of the solvent used (35,36). Along with a polar mechanism (37), a metal-complex-induced mechanism involving a free-radical intermediate has been proposed.



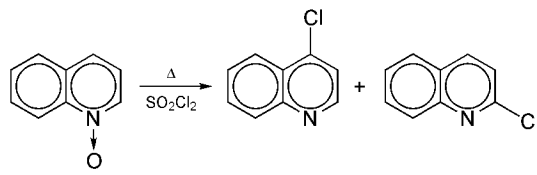
Substitution Reactions. Aromatic heterocyclic *N*-oxides undergo both electrophilic and nucleophilic substitution because the dipolar *N*-oxide group is both an electron donor and an electron acceptor, giving rise to the resonance structures:



Pyridine oxide [694-59-7] is converted to 4-nitropyridine oxide in 80–90% yield on heating with concentrated sulfuric acid and fuming nitric acid at 100°C (38).



Nucleophilic substitution occurs in positions α and γ to the *N*-oxide group. In nearly all these reactions deoxygenation occurs giving the substituted heterocyclic amine.



Heterocyclic *N*-oxides can react at the oxygen atom with a variety of electrophilic reagents to give adducts which, according to the reagent and reaction conditions, may be stable or react further (39). Heterocyclic *N*-oxides are reduced by reaction of nucleophiles at the *N*-oxide oxygen.

Manufacturing and Processing

Linear alpha-olefins are the source of the largest volume of aliphatic amine oxides. The olefin reacts with hydrogen bromide in the presence of peroxide catalyst, to yield primary alkyl bromide, which then reacts with dimethylamine to yield the corresponding alkyl dimethylamine. Fatty alcohols and fatty acids are also used to produce amine oxides (Fig. 1).

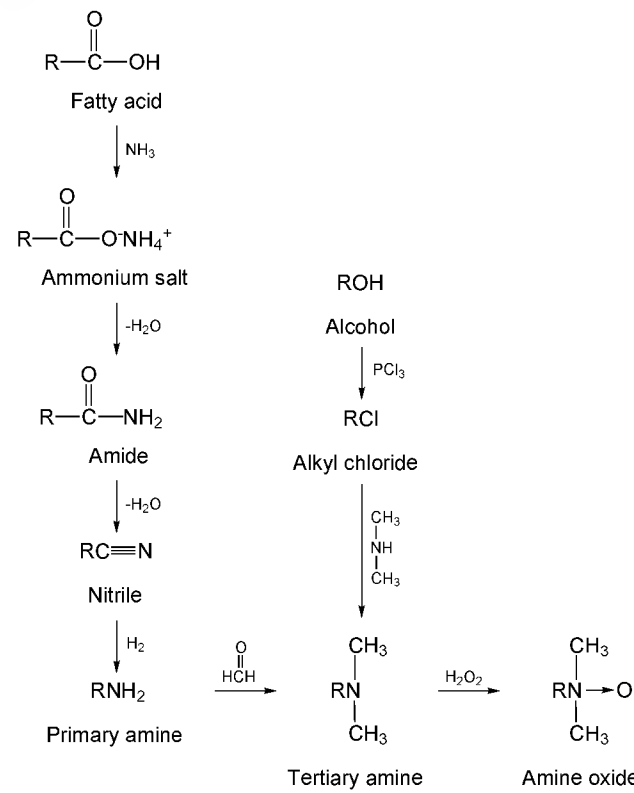


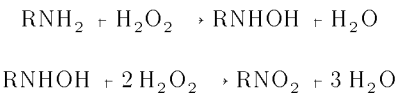
Fig. 1. Routes to tertiary amines from fatty acids or fatty alcohols.

Amine oxides used in industry are prepared by oxidation of tertiary amines with hydrogen peroxide solution using either water or water and alcohol solution as a solvent. A typical industrial formulation is as follows:

<i>N,N</i> -dimethyltetradecylamine [112-75-4]	1475 kg
hydrogen peroxide (35%)	640 kg
EDTA	1.5 kg
water	3225 kg

EDTA (ethylenediaminetetraacetic acid, [60-00-4]) chelates any trace metals that would otherwise decompose the hydrogen peroxide [7722-84-1]. The amine is preheated to 55–65°C and the hydrogen peroxide is added over one hour with agitation; the temperature is maintained between 60–70°C. The reaction is exothermic and cooling must be applied to maintain the temperature below 70°C. After all the peroxide has been added, the temperature of the reaction mixture is raised to 75°C and held there from three to four hours until the unreacted amine is less than 2.0% . The solution is cooled and the unreacted hydrogen peroxide can be destroyed by addition of a stoichiometric amount of sodium bisulfite. This may not be desirable if a low colored product is desired, in which case residual amounts of hydrogen peroxide enhance long-term color stability.

Primary and secondary amines are oxidized to the respective hydroxyl amines, and further oxidation to the nitro compound occurs in the case of primary amines.



Owing to the lower basicity of the parent amines, aromatic amine oxides cannot be formed directly by hydrogen peroxide oxidation. These compounds may be obtained by oxidation of the corresponding amine with a peracid; perbenzoic, monoperphthalic, and monopermaleic acids have been employed.

Uses

Detergents. Aliphatic amine oxides find wide use in the detergent and personal care industries. A comparison of detergents and admixtures with other surfactants in a light duty liquid detergent revealed that the most effective performance came from a blend of ammonium ether sulfate and an alkyl dimethylamine oxide where the alkyl group contained 14 carbon atoms (40). Amine oxides improve the stability and amount of foam generated in light liquid detergents and because of this they are used extensively in shampoos, dishwashing liquids, and liquid soaps. Other uses for amine oxides are found in paper and textile production, electroplating, oil and petroleum, plastics and rubber, metal and mining, polymerization, and photographic industries.

Amine oxides compete with alkanolamides as foam boosters in the detergent and personal care industry. Although amine oxides are more expensive than alkanolamides they have the advantage of being milder to the skin and eyes and are more effective surfactants, so that on a cost performance basis they are a better buy than alkanolamides in many cases (see ALKANOLAMINES FROM OLEFIN OXIDES AND AMMONIA). As well as being excellent foam stabilizers in liquid detergents, alkyl amine oxides also increase viscosity, emolliency, detergency, and antistatic properties in many detergent and cosmetic formulas (41).

The surface active properties of aliphatic amine oxides were discovered in the 1930s and the wetting, detergent, emulsion, and foam stabilizing properties were published shortly thereafter (42). However, the use of amine oxides was not significant until Procter and Gamble started using them in household products around 1960 (43–46).

Organic Reagents. Amine oxides are used in synthetic organic chemistry in the preparation of olefins, or phase-transfer catalysts (47), in alkoxylation reactions (48), in polymerization, and as oxidizing agents (49,50).

Textiles. In the area of textile and synthetic fiber processing, amine oxides have been used as dyeing auxiliaries as well as wetting agents (51,52), as antistatic agents (qv) (53–55), and as bleaching agents (56,57).

Pharmaceutical Uses. The biochemistry of heteroaromatic amine oxides has been extensively explored and has led to the synthesis of many biochemically and pharmaceutically important compounds (58). Aromatic amine oxides are useful as analgesics, antihistamines, antitussives, diuretics, tranquilizers, and drug potentiators. In many cases, the *N*-oxides of pharmacologically active tertiary amines have added benefits, ranging from lower toxicity and better solubility to enhanced therapeutic behavior. The biological activity of these materials has led to patented uses as bactericides, fungicides, insecticides, nematocides, filaricides, amoebicides, anthelmintics, antiparasitics, and disinfectants. The pharmacology and biochemistry of amine oxides has been reviewed (59). Earlier references covering these and other applications were reported in a survey on amine oxides by the Du Pont Company (60).

Other. Other uses of aliphatic amine oxides are as corrosion inhibitors for nonferrous metals (61) and also as fuel oil antiicing and pourpoint additives that also depress combustion chamber fouling (62–64), in the plastic industry as molecular weight regulators in ethylene and propylene copolymerization (65), in photography to prevent waterspots in drying photographic films (66), and as complexing developers and dyes (67).

Economic Aspects

The major producers of fatty amine oxides are Jordon Chemical Company, Procter and Gamble, Lonza, Stepan, Sherex Chemicals, and Akzo Chemicals Inc. It is estimated that 13,600 t of amine oxides were purchased for end use in the United States in 1987 (68). Of this amount around 80% was consumed in various household products, and 10% in industrial, institutional, and commercial applications. These figures do not include the estimated 27,000 –32,000 t of amine oxides produced by Procter and Gamble for captive use.

Specifications

Industrial specifications for aliphatic tertiary amine oxides generally require an amine oxide content of 20–50% . These products may contain as much as 5% unreacted amine, although normally less than 2% is present. Residual hydrogen peroxide content is usually less than 0.5% . The most common solvent systems employed are water and aqueous isopropyl alcohol, although some amine oxides are available in nonpolar solvents. Specifications for individual products are available from the producers.

Analytical Methods

Analytical methods include thin-layer chromatography (69), gas chromatography (70), and specific methods for determining amine oxides in detergents (71) and foods (72). Nuclear magnetic resonance (73–75) and mass spectrometry (76) have also been used. A frequently used procedure for industrial amine oxides (77) involves titration with hydrochloric acid before and after conversion of the amine to the quaternary ammonium salt by reaction with methyl iodide. A simple, rapid quality control procedure has been developed for the determination of amine oxide and unreacted tertiary amine (78).

Health and Safety Factors

Aliphatic amine oxides such as alkyl dimethylamine oxides and alkylbis(2-hydroxyethyl)amine oxides range from practically nontoxic to slightly toxic (79). Reported LD₅₀s range from 1.77 g/kg to 6.50 g/kg. The commercial concentrated products are primary skin and eye irritants. At concentrations of 2% , these products may be considered as nonirritating to the skin or eye.

Test	Result
bacterial toxicity, Bringmann-Kuhn	EC ₁₀ = 80 ppm
algae toxicity, growth inhibition 72 h	EC ₅₀ = 0.66 ppm
	NOEC = 0.25 ppm
daphnia toxicity, acute 48 h	EC ₅₀ = 9.5 ppm
	NOEC = 4.6 ppm
fish toxicity (zebra fish), acute 96 h	LC ₅₀ = 42.0 ppm
	NOEC = 33.5 ppm
biodegradation, Closed Bottle, 28 d	readily = 93%

Among the aromatics, it was found that 4-nitroquinoline *N*-oxide [56-57-5] is a powerful carcinogen producing malignant tumors when painted on the skin of mice (80). It was further established that the 2-methyl, 2-ethyl, and 6-chloro derivatives of 4-nitroquinoline oxide are also carcinogens (81).

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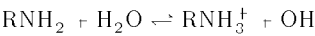
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AMINES

Lower aliphatic amines,
Cycloaliphatic amines,
Fatty amines,
Aromatic amines,

LOWER ALIPHATIC AMINES

Lower aliphatic amines are derivatives of ammonia with one, two, or all three of the hydrogen atoms replaced by alkyl groups of five carbons or less. Amines with higher alkyl groups are known as fatty amines. The name, chemical formula, molecular weight, CAS Registry Number, and common name or abbreviation of commercially important amines are given in Table 1. Amines are toxic, colorless gases or liquids, highly flammable, and have strong odors. Lower mol wt amines are water soluble and are sold as aqueous solutions and in pure form. Amines react with water and acids to form alkylammonium compounds analogous to ammonia. The base strengths in water of the primary, secondary, and tertiary amines and ammonia are essentially the same, as shown by the equilibrium constants. Values of K_b for some individual amines are given in Table 2.



Primary and secondary amines can also act as very weak acids ($K_a \sim 10^{-33}$). They react with acyl halides, anhydrides, and esters with rates depending on the size of the alkyl group(s). With carbon disulfide and carbon dioxide, these amines form alkyl ammonium salts of dithiocarbamic and carbamic acid, respectively, and with isocyanic acid and alkyl or aryl isocyanates, substituted ureas. Reaction with isothiocyanate gives the corresponding thioureas. Primary amines give alcohols with nitrous acid, secondary amines give highly toxic nitrosamines (see *N-NITROSAMINES*). The lower aliphatic amines are widely used as intermediates in the manufacture of medicinal, agricultural, textile, rubber, and plastic chemicals.

Table 1. Commercial Alkylamines

Alkylamine	CAS Registry Number	Molecular formula	mol wt	Synonym or common abbreviation
methylamine	[74-89-5]	CH ₅ N	31.06	monomethylamine, aminomethane, MMA
dimethylamine	[120-40-3]	C ₂ H ₇ N	45.08	DMA
trimethylamine	[75-50-3]	C ₃ H ₉ N	59.11	<i>N,N</i> -dimethylmethanamine, TMA
ethylamine	[74-04-7]	C ₂ H ₇ N	45.08	monoethylamine, aminoethane, MEA
diethylamine	[109-89-7]	C ₄ H ₁₁ N	73.14	Diethanamine, <i>N</i> -ethylethanamine, DEA
triethylamine	[121-44-8]	C ₆ H ₁₅ N	101.19	TEA
<i>n</i> -propylamine	[107-10-8]	C ₃ H ₉ N	59.11	mono- <i>n</i> -propylamine, 1-amino-propane, propanamine, MNPA
di- <i>n</i> -propylamine	[142-84-7]	C ₆ H ₁₅ N	101.19	<i>N</i> -propyl-1-propanamine, DNPA
tri- <i>n</i> -propylamine	[102-69-2]	C ₉ H ₂₁ N	143.27	<i>N,N</i> -dipropyl-1-propanamine, TNPA
isopropylamine	[75-31-0]	C ₃ H ₉ N	59.11	2-aminopropane, MIPA
diisopropylamine	[108-18-9]	C ₆ H ₁₅ N	101.19	<i>N</i> -(1-methylethyl)-2-propanamine, DIPA
allylamine	[107-11-9]	C ₃ H ₇ N	57.10	monoallylamine, 3-aminopropene
diallylamine	[124-02-7]	C ₆ H ₁₁ N	97.16	
triallylamine	[102-70-5]	C ₉ H ₁₅ N	137.22	
<i>n</i> -butylamine	[109-73-9]	C ₄ H ₁₁ N	73.14	mono- <i>n</i> -butylamine, 1-aminobutane, MNBA
di- <i>n</i> -butylamine	[111-92-2]	C ₈ H ₁₉ N	129.24	<i>N</i> -butyl-1-butanamine, DNBA
tri- <i>n</i> -butylamine	[102-82-9]	C ₁₂ H ₂₇ N	185.35	TNBA
isobutylamine	[78-81-9]	C ₄ H ₁₁ N	73.14	monoisobutylamine, 1-amino-2-methylpropane, MIBA
diisobutylamine	[110-96-3]	C ₈ H ₁₉ N	129.24	2-methyl- <i>N</i> -(2-methylpropyl)-1-propanamine, DIBA
triisobutylamine	[1116-40-1]	C ₁₂ H ₂₇ N	185.35	TIBA
<i>sec</i> -butylamine	[13952-84-6]	C ₄ H ₁₁ N	73.14	2-aminobutane, 1-methylpropanamine
<i>t</i> -butylamine	[75-64-9]	C ₄ H ₁₁ N	73.14	2-aminoisobutane, 1,1-dimethylethanamine, trimethylaminomethane
ethyl- <i>n</i> -butylamine	[13360-63-9]	C ₆ H ₁₅ N	101.19	EBA
dimethyl- <i>n</i> -butylamine	[927-62-8]	C ₆ H ₁₅ N	101.19	DMBA
<i>n</i> -amylamine	[110-58-7]	C ₅ H ₁₃ N	87.16	
di- <i>n</i> -amylamine	[2050-92-2]	C ₁₀ H ₂₃ N	157.30	dipentylamine, dipentanamine
tri- <i>n</i> -amylamine	[621-77-2]	C ₁₅ H ₃₃ N	227.43	tripentylamine, tripentanamine

Table 2. Alkylamine Physical Properties^a

Alkylamine	Mp, °C	Bp, °C	Vapor pressure at 20°C, kPa ^b	Density ^c	Refractive index ^d	Water solubility, g/100 g H ₂ O	$K_b \cdot 10^4$
methylamine	93.0	6.3	288	0.67	1.351	108 (25°C)	4.26
dimethylamine	93.0	6.9	170	0.656	1.347	163 (40°C)	6.03
trimethylamine	−117.0	2.9	191	0.633	1.3449	89 (30°C)	0.63
ethylamine	−81.0	16.6	116	0.683 ^e	1.3663		5.62
diethylamine	−50.0	55.9	25.9	0.7062 ^e	1.3823		1.29
triethylamine	−114.7	88.8	7.2	0.729 ^e	1.401	5.5 (30°C)	5.75

<i>n</i> -propylamine	83.0	47.8	33.9	0.718 ^e	1.3879		2.51
di- <i>n</i> -propylamine	40.0	109.3	2.8	0.7401 ^e	1.4042		7.9
tri- <i>n</i> -propylamine	93.5	151.0	0.3	0.7567	1.414		
isopropylamine	95.2	32.4	63.7	0.689 ^e	1.3742		4.27
diisopropylamine	61.0	83.9	8	0.7178 ^e	1.3924	sl sol	3.72
allylamine	88.2	52.9		0.7627	1.42		0.53
diallylamine	88.4	110.4		0.7874	1.44	5.6	0.13
triallylamine	70.0	149.5		0.80	1.45	0.25	0.018
<i>n</i> -butylamine	50.0	77.8	9.6	0.74	1.4031		4.07
di- <i>n</i> -butylamine	61.9	159.6	0.3	0.76	1.4177	0.47	5.12
tri- <i>n</i> -butylamine	< 70	214.0		0.78 ^e	1.4297	sl sol	
isobutylamine	85.5	68.5	13.3	0.736 ^e			
diisobutylamine	70.0	139.5	1.3	0.745	1.409	sl sol	
triisobutylamine	21.8	191.5		0.7684	1.4252		
<i>sec</i> -butylamine	104.5	63.0	20.0	0.7246	1.3932	sol	
<i>t</i> -butylamine	72.7	44.5		0.69 ^f	1.375 ^g		4.07
ethyl- <i>n</i> -butylamine	78.0	111.0	2.4	0.7398	1.404		
dimethyl- <i>n</i> -butylamine		95.0		0.7206	1.397		
<i>n</i> -amylamine	55.0	104.5		0.7547	1.4118		
di- <i>n</i> -amylamine		202–203		0.7771	1.4272	sl sol	
tri- <i>n</i> -amylamine		240–245		0.7907	1.43665	insol	

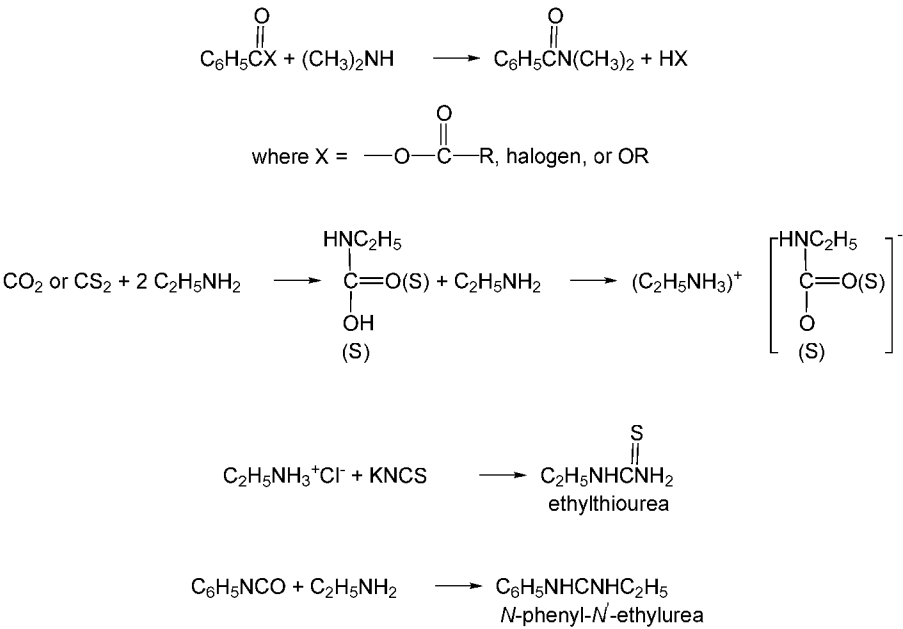
^a Refs. 1, 2.
^b To convert kPa to mm Hg, multiply by 7.5.
^c n_{D}^{20} unless otherwise noted.
^d n_{D}^{20} unless otherwise noted.
^e d_{20}^{20}
^f d_{25}^{25}
^g n_{D}^{25}

Physical Properties

Table 2 lists the physical properties of the commercially important alkylamines. The fishy odor of methylamines increases from mono- to trimethylamine. In high concentrations, they all have the odor of ammonia. On cooling aqueous solutions, the crystalline hydrates, CH₃NH₂·3H₂O, (CH₃)₂NH·7H₂O, and (CH₃)₃N·10H₂O are formed. Methylamine solutions are good solvents for many inorganic and organic compounds. At atmospheric pressure, trimethylamine forms minimum-boiling azeotropes with ammonia and other methylamines. With increasing pressure, the trimethylamine content of the azeotrope decreases and none is formed above 2652 kPa (370 psig). At atmospheric pressure, trimethylamine boils lower than dimethylamine; this order is reversed at about 446 kPa (50 psig).

Thermodynamic data are available only for the lower alkylamines, mainly estimates based on a few experimental determinations (3,4). Many manufacturing processes appear to be limited by thermodynamic equilibria. The lack of accurate free energy data for these amines limits the application of thermodynamic considerations, in contrast to the situation in hydrocarbon technology.

Chemical Properties The formation of salts with acids is the most characteristic reaction of amines. Since the amines are soluble in organic solvents and the salts are usually not soluble, acidic products can be conveniently separated by the reaction with an amine, the unshared electron pair on the amine nitrogen acting as proton acceptor. Amines are good nucleophiles; reactions of amines at the nitrogen atom have as a first step the formation of a bond with the unshared electron pair of nitrogen, eg, reactions with acid anhydrides, halides, and esters, with carbon dioxide or carbon disulfide, and with isocyanic or isothiocyanic acid derivatives.



Oxidation by various means gives a wide variety of products. Tertiary aliphatic amines form *N*-oxides with hydrogen peroxide or peracids. Secondary or primary amines give amine oxide intermediates which rearrange to hydroxylamines. Since the hydroxylamines are easily oxidized to nitro compounds, mixtures are usually obtained (see AMINE OXIDES). The oxidation of amines by the oxides of nitrogen leads to various products, depending on the amine and the experimental conditions. Nitrous acid (HONO) can be used to determine whether an amine is primary, secondary, or tertiary. Primary amines evolve nitrogen; secondary amines give yellow liquids or solids (*N*-nitroso compounds); tertiary aliphatic amines react without evolution of gas and usually give a

complex mixture of products. Since the *N*-nitrosamines have been classified as potential carcinogens, there is considerable concern about contamination of air with amines. Certain oxides of nitrogen, N₂O₃, N₂O₄, and NO plus air, react rapidly with amines to form nitrosamines under alkaline conditions (5).

Allylamines are somewhat unique in that both amine and olefin functionalities are available. This allows the allylamines to find uses in many areas where the simpler alkylamines are not suitable, eg, taking advantage of the double bond to form polymeric ammonium salts used as flocculating agents (see ALLYL MONOMERS AND POLYMERS).

Monobutylamines are easily soluble in water and hydrocarbons and can generally be steam distilled. These properties lead to uses in soaps for water and oil emulsions, and as corrosion inhibitors in steam boiler applications (see CORROSION AND CORROSION INHIBITORS; EMULSIONS). Morpholine is also extensively used as a corrosion inhibitor in steam boiler systems. In addition, it is widely used as an intermediate in the production of delayed-action rubber accelerators.

Alkylamines are corrosive to copper, copper-containing alloys (brass), aluminum, zinc, zinc alloy, and galvanized surfaces. Aqueous solutions of alkylamines slowly etch glass as a consequence of the basic properties of the amines in water. Carbon or stainless steel vessels and piping have been used satisfactorily for handling alkylamines and, as noted above, some alkylamines can act as corrosion inhibitors in boiler applications.

Manufacture

Lower aliphatic amines can be prepared by a variety of methods, using many different types of raw materials. By far the largest commercial applications involve the reaction of alcohol with ammonia to form the corresponding amines. Other methods are employed depending on the particular amine desired, raw material availability, plant economics, and the ability to sell co-products. The following manufacturing methods are used commercially to produce the lower alkylamines. Table 5 gives plant and capacity information for these methods.

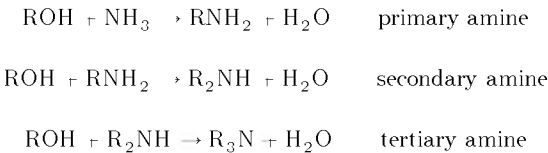
- Method 1. Alcohol amination—acid catalyzed: high temperature amination of an alcohol over a solid acid catalyst.
- Method 2. Alcohol amination—metal catalyzed: amination of an alcohol over a metal catalyst under reducing conditions.
- Method 3. Reductive alkylation: reaction of an amine or ammonia and hydrogen with an aldehyde or ketone over a hydrogenation catalyst.
- Method 4. Ritter reaction: reaction of hydrogen cyanide with an olefin in an acidic medium to produce a primary amine.
- Method 5. Nitrile reduction: reaction of a nitrile with hydrogen over a hydrogenation catalyst.
- Method 6. Olefin amination: reaction of an olefin with ammonia.
- Method 7. Alkyl halide amination: reaction of ammonia or alkylamine with an alkyl halide.

Alcohol Amination. There are many similarities in the process technologies for Methods 1 and 2. In both, an alcohol reacts with ammonia over a fixed catalyst bed at elevated temperature. The reaction section consists of feed systems, vaporizers, and or preheaters which pass a liquid or gaseous feed mixture over the catalyst bed in the desired ratio, temperature, and pressure. Possible amination catalysts for each method are as follows.

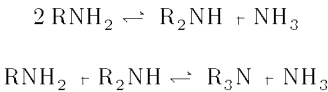
- Method 1: silica—alumina, silica, alumina, titania, tungstic oxides, phosphates, zeolites, and clays.
- Method 2: cobalt, nickel, copper, and copper chromite.

Alcohol amination reactions are described by a network of two general types of reaction.

- (1) Sequential substitution reactions which transform alcohols into a family of primary, secondary, and tertiary amines.



- (2) Reforming reactions which equilibrate the alkylamines.



To manufacture the lower alkylamines by Method 1, ammonia and alcohol are passed continuously over a fixed bed containing the catalyst in a gas—solid heterogeneous reaction. The ammonia to alcohol mole ratio varies from 2:1 to 6:1 depending on the amine desired as shown in Figure 1. Operating conditions are maintained in the range from 300–500°C and 790–3550 kPa (100–500 psig) at a gas hourly space velocity between 500–1500 vol vol per hour. Yields are typically in excess of 90%.

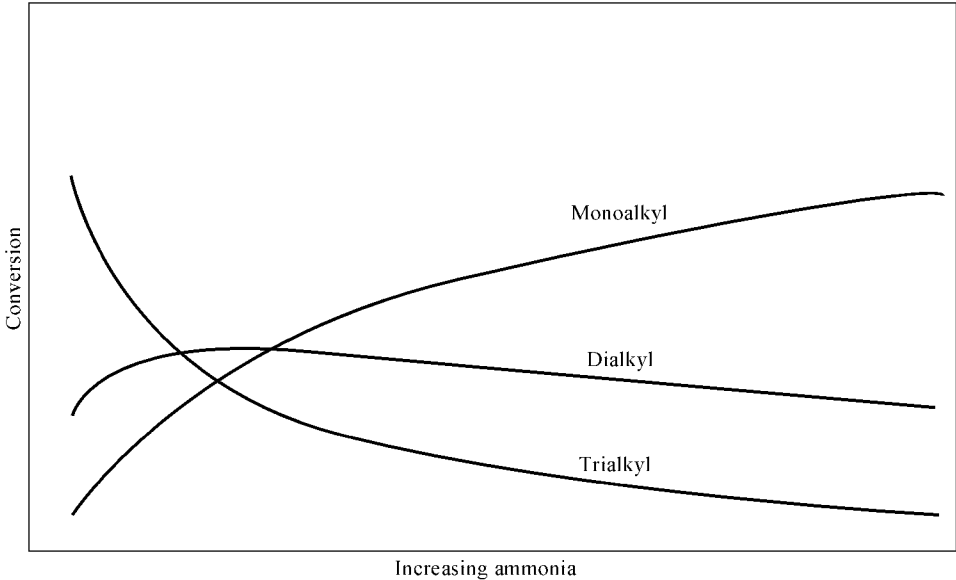


Fig. 1. Amine distribution general behavior. Converted alcohol to amine product as the ammonia to alcohol ratio increases.

In Method 2, hydrogen is also passed over the catalyst to prevent it from deactivating (6). The mole ratio of hydrogen is typically in the range of 1 to 2.5:1 with respect to the alcohol. Operating conditions are maintained in the range 130–250°C. As in Method 1, yields are usually in the 90% range.

Water is a by-product of the amination reactions in both methods. The mixture of ammonia, water, unconverted alcohol, and amines are

continuously separated by distillation. Ammonia, unconverted alcohol, and any amines produced in excess of anticipated sales are recycled to the reactor section. A schematic depicting the typical process flows is presented as Figure 2. Note that the separation requirements vary from process to process depending on the by-products and product specifications.

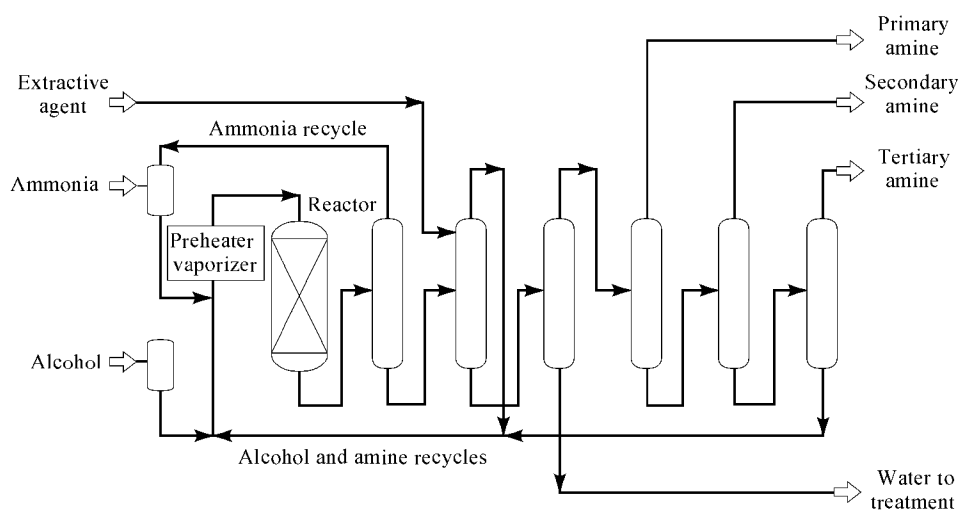
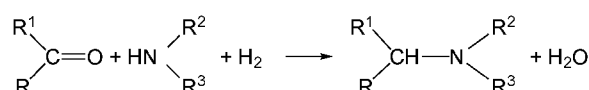


Fig. 2. Typical amination reactor and separation train.

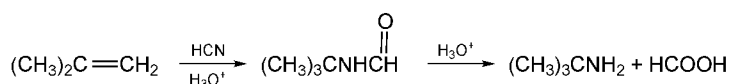
Reforming of the amines produced in excess of anticipated sales is practiced commercially using both types of catalyst. Recent technological efforts have been directed at using zeolites to avoid an equilibrium product distribution. The zeolites can be used to conduct amination reactions via Method 1. The size of the zeolite pore openings to and from the catalytically active cages limits the production of the tertiary amine. Primary and secondary amines are produced using the zeolite, but the rate at which the tertiary amine is produced may be severely retarded. Studies on the formation of methylamines from methanol best illustrate this technology (7–10).

Reductive Alkylation (Method 3). Ammonia or a primary or secondary amine, hydrogen, and an aldehyde or ketone form aliphatic amines when they react over a hydrogenation catalyst, eg, nickel, cobalt, copper chromite, platinum, or palladium. These reactions may be carried out at conditions similar to Method 2 and in similar equipment. Liquid-phase stirred-tank equipment operated either continuously or batch is also an option. A larger exothermic heat of reaction is involved which limits fixed-bed applications to those with a large excess of ammonia, which acts as a heat sink, limiting the total bed temperature rise. Alternatively, a multistage reactor with interstage cooling or a multitubular reactor with cooling to remove the heat of reaction may be employed, but this increases the cost and operating complexity of the reactor. The heat removal problem is more readily controlled in stirred tank systems with cooling coils or systems which pump the reaction mass through external heat exchangers, eg, loop reactors. Typically these reactions take place at lower temperatures than alcohol amination, and reforming reactions compete less favorably with the reductive alkylation. Consequently, it is quite often possible to control the selectivity to a single product through the judicious choice of catalyst and of the mole ratio of the starting aldehyde or ketone to the amine or ammonia. Further it is possible to produce amines with mixed alkyl groups by this method. In the following, R_n = alkyl or H.



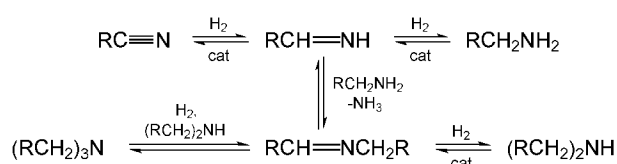
Operating conditions vary radically depending on the type of equipment selected but typically temperatures used are in the range of 50 to 180°C and pressures of 446 to 3550 kPa (50 to 500 psig) are sufficient (11).

Ritter Reaction (Method 4). A small but important class of amines are manufactured by the Ritter reaction. These are the amines in which the nitrogen atom is adjacent to a tertiary alkyl group. In the Ritter reaction a substituted olefin such as isobutylene reacts with hydrogen cyanide under acidic conditions (12). The resulting formamide is then hydrolyzed to the parent primary amine. Typically sulfuric acid is used in this transformation of an olefin to an amine. Stoichiometric quantities of sulfate salts are produced along with the desired amine.



The only low molecular weight alkylamine produced by this method commercially is *t*-butylamine.

Nitrile Reduction (Method 5). The reduction of nitriles with hydrogen to simple alkylamines is another commercially practiced technology (13). As with Method 3, both continuous packed-bed reactor systems designed for removal of the heat of reaction or batch stirred tank or loop reactor systems may be used. Catalysts for this transformation are nickel, cobalt, platinum, palladium, and rhodium. Again the operating conditions vary widely, depending on the type of equipment; but temperatures and pressures are generally in the range, 50–150°C, and 446–73,900 kPa (50–2000 psig), respectively. Selectivity to primary amine is normally controlled by introducing ammonia as a diluent and nickel or cobalt as catalyst.



Secondary and tertiary amines are preferentially produced when rhodium or palladium are chosen as catalyst. As in Method 3, reforming reactions do not normally compete with the hydrogenation reaction and high selectivities to the desired product are possible.

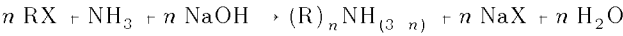
Olefin Amination (Method 6). The most recent technology for the production of lower alkylamines is olefin amination (14). This is zeolite-catalyzed reaction of ammonia with an olefin, eg, isobutylene, and is practiced in a packed-bed reactor system in the vapor phase.



A number of zeolitic materials have been claimed to catalyze this reaction and reaction temperatures are on the order of 200–350°C with pressures as high as 18000 kPa (2600 psi) reported. This is a low conversion process and recycle of the unconverted starting materials is necessary to provide an economical process. Amination of ethylene to produce ethylamines catalyzed by ammonium iodide is reported, but not believed to be practiced commercially (15,16).

Alkyl Halide Amination (Method 7). The oldest technology for producing amines is the reaction of ammonia with an alkyl halide. This

method is still of commercial importance for the manufacture of allylamines and select mixed alkylamines. Allylamines are not readily made by the other methods mentioned here primarily because either the double bond in the allylamine becomes saturated (methods involving hydrogen) or the severe reaction conditions result in cyclization or polymerization by-products (17). Alkyl halide amination occurs under very mild conditions, typically with the addition of aqueous alkali to neutralize the hydrogen halide coproduced by the reaction. As in the Ritter reaction, stoichiometric quantities of salt are produced. The resulting waste disposal problem detracts from the general utility and popularity of this and the Ritter reaction.



Where the value of *n* denotes a 1°, 2°, or 3° amine.

Shipment and Handling

The methylamines and ethylamine have vapor pressures above atmospheric at ambient temperatures and are available in the pure form only in pressurized containers. These amines are also sold as aqueous solutions with vapor pressures below atmospheric for ease of handling. Diethylamine, triethylamine, and all of the higher mol wt amines are sold as the pure compounds.

Anhydrous methylamines and ethylamine are considered flammable gases. They are shipped under pressure (239 –446 kPa, 20–50 psig) and are available in bulk tank trucks and railcars. Aqueous solutions of the methylamines and ethylamine are considered flammable liquids and are available in drums, bulk tank trucks, and railcars. Most of the other higher amines are considered flammable or combustible liquids. All the lower alkylamines are also considered toxic and have strong odors.

The Department of Transportation requires labelling of all shipments of amines commensurate with the associated hazards. Amine shipments are regulated by the Coast Guard, the DOT, and the International Air Transport Association. Aliphatic amines are stored satisfactorily in carbon steel and stainless steel, but are corrosive to copper, aluminum, zinc, and their alloys.

Health and Safety, Toxicology

Alkylamines are toxic. Both the liquids and vapors can cause severe irritations to mucous membranes, eyes, and skin. Protective butyl rubber gloves, aprons, chemical face shields, and self-contained breathing apparatus should be used by all personnel handling alkylamines. Amines are flammable and the lower mol wt alkylamines with high vapor pressures at ordinary temperatures have low flash points. Amines should be handled in well-ventilated areas only after eliminating potential sources of ignition.

Alkylamines should be stored away from oxidizing agents and acids because of incompatibility. Contact with these chemicals gives a rapid and exothermic reaction.

Threshold limit values (TLV) adopted by the ACGIH are guidelines for the control of health hazards. Table 3 shows the eight-hour TWA and the STEL TLV values for those lower alkylamines listed in the ACGIH guideline (18).

Table 3. ACGIH Threshold Limit Values

Alkylamine	TWA, ppm	STEL, ppm
methylamine	10	
dimethylamine	10	
trimethylamine	10	15
ethylamine	10	
diethylamine	10	25
isopropylamine	5	10
diisopropylamine ^a	5	
<i>n</i> -butylamine ^{a,b}	5	15
morpholine ^a	20	30

^a Skin exposure should be avoided and must be considered when selecting protective equipment and clothing.

^b The TLV listed is a ceiling limit and should never be exceeded.

Economic Aspects, Specifications, and Uses

Table 4 gives information on significant uses and Table 5 provides manufacturing data on various alkylamines for 1988, from capacity announcements in *Chemical Week*, *Hydrocarbon Processing*, and *European Chemical News*. Table 6 gives general sales specifications and the U.S. list price (1991). More detailed product specifications are available from the various indicated manufacturers.

Table 4. Products Manufactured Using Alkylamines

Chemical name	CAS Registry Number	Trade name common name	Use
<i>From Monomethylamine</i>			
3,7-dihydro-1,3,7-trimethyl-1 <i>H</i> -purine-2,6-dione	[58-08-2]	Caffeine	stimulant, diuretic
3,7-dihydro-1,3-dimethyl-1 <i>H</i> -purine-2,6-dione	[58-55-9]	Theophylline	antispasmodic
1-naphthyl- <i>N</i> -methylcarbamate	[63-25-2]	Sevin carbaryl	insecticide
sodium <i>N</i> -methylthiocarbamate	[137-42-8]	Vapam metham	pesticide
ethyl 1-methyl-4-phenylpiperidine-4-carboxylate	[57-42-1]	Demerol	analgesic
<i>p</i> - <i>N</i> -methylaminophenol sulfate	[55-55-0]	Metol	photographic developer
2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate	[1563-66-2]	Furadan	systemic insecticide
<i>N</i> -methyl-2-pyrrolidone	[872-50-4]		solvent, paint stripper
monomethylammonium nitrate	[22113-87-7]	Tovex	water gel explosive
/			
2-methyl-2-(methylthio)-propanal <i>O</i> -[(methylamino)-carbonyl]oxime	[116-06-3]	Temik aldicarb	insecticide
methyl- <i>N</i> -{[(methylamino)carbonyl]oxy}-ethanimidothioate	[16752-77-5]	Lannate methomyl	insecticide
/			
<i>N,N</i> -dimethyl-2-methylcarbamoyloxyimino-2-(methylthio)acetamide	[23135-22-0]	Vydate oxamyl	insecticide
/			
2,2-dimethylbenzo-1,3-dioxol-4-ol- <i>N</i> -methyl carbamate	[22781-23-3]	Ficam bendiocarb	pesticide
/			

<i>N</i> -[5(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]- <i>N,N</i> -dimethylurea	[34014-18-1]	Spike tebuthiuron	herbicide
2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione	[20354-26-1]	Probe metazole	herbicide
methyl isothiocyanate	[556-61-6]		fungicide nematocide
2-methylaminoethanol	[109-83-1]		electrostatic automotive coatings, acid gas scrubbing
	<i>From Dimethylamine</i>		
dimethyldithiocarbamate zinc salt	[137-30-4]	Ziram	fungicide, rubber processing
dimethyldithiocarbamate iron salt	[14484-64-1]	Ferbam	fungicide, rubber processing
bis(dimethylthiocarbamoyl) disulfide	[137-26-8]	Thiram	rubber accelerator
tetramethylthiuram monosulfide	[63797-03-5]	Monex, Thionex	rubber accelerator
1,1-dimethylhydrazine	[57-14-7]	UDMH	propellant
2-dimethylaminoethyl- <i>p</i> -butylaminobenzoate hydrochloride	[136-47-0]	Pantocaine	anesthetic
2-(benzhydryloxy)- <i>N,N</i> -dimethylethylamine-HCl	[147-24-0]	Benadryl	antihistaminic
dimethylformamide	[68-12-2]		solvent
dimethylacetamide	[127-19-5]		solvent
1,3,5-tris(dimethylaminomethyl)phenol	[90-72-2]	DMP-30, Amicore TMR30	urethane catalyst
stearyl dimethylbenzylammonium chloride	[122-19-0]	Triton X-400	surfactant
lauryl dimethylamine	[112-18-5]		surfactant
copolymers of dimethyldiallyl ammonium chloride and acrylates or acrylamides		DMDAC, DADMAC, DADM	water treatment
epichlorohydrin-dimethylamine based polymers		epi-DMA	water treatment
alkyl(C ₁₀ –C ₁₈)dimethylamine oxides			nonionic detergent
alkyl(C ₁₀ –C ₁₈)benzyl dimethylammonium salts			germicides
3-(3,4-dichlorophenyl)-1,1-dimethylurea	[330-54-1]	Karmex diuron	herbicide
3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazin-2,4-(1 <i>H</i> ,3 <i>H</i>)dione	[51235-04-2]	Velpar hexazinone	herbicide
2-dimethylaminoethyl methacrylate	[2867-47-2]		water treatment
			dispersant pH control for water-based coatings
			surfactants, liquid soaps, water treatment
3-dimethylaminopropylamine	[109-55-7]		epoxy resin accelerator
benzyl dimethylamine	[108-83-3]		
	<i>From Trimethylamine</i>		
trimethylamine	[75-50-3]		acid scavenger for nylon and benzyl ester production
			animal feed supplement
choline chloride	[67-48-1]		ion-exchange resin
cross-linked polystyrene functionalized with alkyltrimethylammonium groups	[53664-47-4]	Amberlyst, Dowex	
benzyltrimethylammonium hydroxide	[100-85-6]	Triton B	base catalyst, dye leveling agent, polyester gelling inhibitor
	<i>From Monoethylamine</i>		
2-chloro-4-ethylamino-6-isopropyl-amino-1,3,5-triazine	[1912-24-9]	Atrazine	herbicide
2-chloro-4-(1-cyano-1-methylethyl-amino)-6-ethylamino-1,3,5-triazine	[21725-46-2]	Bladex cyanazine	herbicide
2-ethylamino-4-isopropylamino-6-methylthio-1,3,5-triazine	[834-12-8]	Evik ametryn	herbicide
2-chloro-4,6-bis(ethylamino)-1,3,5-triazine	[122-34-9]	Princep simazine	herbicide
2- <i>t</i> -butylamino-4-ethylamino-6-methylthio-1,3,5-triazine	[886-50-0]	Terbutryn	herbicide
2,4-bis(ethylamino)-6-methylthio-1,3,5-triazine	[1014-70-6]	Simetryn	herbicide
<i>S</i> -ethyl- <i>N</i> -ethyl- <i>N</i> -cyclohexyl thiocarbamate	[1134-23-2]	Cycloate	herbicide
<i>N</i> -ethyl- <i>o,p</i> -toluenesulfonamide	[8047-99-2]	Santicizer 8	plasticizer
	<i>From Diethylamine</i>		
2-diethylaminoethanol	[100-37-8]		corrosion inhibitor, water-based coatings
			adhesion promoter in acrylic coatings
2-diethylaminoethyl methacrylate	[105-16-8]		
<i>N,N</i> -diethyldithiocarbamate salts			
triethylamine salt	[2391-78-8]		rubber accelerator
diethylamine salt	[1518-58-7]		
sodium salt	[148-18-5]		
tetraethylthiuram disulfide	[97-77-8]		rubber accelerator
<i>N,N</i> -diethylhydroxylamine	[3710-84-7]		radical scavenger
<i>N,N</i> -diethyl- <i>m</i> -toluamide	[134-62-3]	DEET	insect repellent
	<i>From Triethylamine</i>		
triethylamine	[121-44-8]		catalyst for foundry-mold resin curing, adhesives, extraction agent in drug synthesis, corrosion inhibitor in paint remover, HCl scavenger in herbicide synthesis
			herbicide
triethylammonium 2-(2,4,5-trichlorophenoxy)propionate	[57213-69-1]	Garlon 3A	herbicide
	<i>From Di-<i>n</i>-propylamine</i>		
α,α,α -trifluoro-2,6- <i>N,N</i> -di- <i>n</i> -propyl- <i>p</i> -tolidine	[1582-09-8]	Treflan trifluralin	herbicide
3,5-dinitro- <i>N,N</i> -di- <i>n</i> -propyl sulfanilamide	[19044-88-3]	Surflan	herbicide

<i>S</i> -ethyl di- <i>n</i> -propyl thiocarbamate	[759-94-4]	Eptam	herbicide
<i>S</i> -propyl dipropyl thiocarbamate	[1929-77-7]	Vernam vernolate	herbicide
<i>From Monoisopropylamine</i>			
2-ethylamino-4-isopropylamino-6-methylthio-1,3,5-triazine	[834-12-8]	Evik ametryn	herbicide
2-chloro-4,6-bis(isopropylamino)-1,3,5-triazine	[139-40-2]	Milogard propazine	herbicide
2-methoxy-4,6-bis(isopropylamino)-1,3,5-triazine	[1610-18-0]	Pramitol prometon	herbicide
2-ethylthio-4,6-bis(isopropylamino)-1,3,5-triazine	[4147-51-7]	Sancap dipropetryn	herbicide
2-chloro-4-(ethylamino)-6-(isopropylamino)-1,3,5-triazine	[1912-24-9]	Atrazine	herbicide
<i>N</i> -(phosphonomethyl)-glycine isopropylamine salt	[38641-94-0]	Roundup glyphosate	herbicide
/			
ethyl 4-(methylthio)- <i>m</i> -tolyl isopropylphosphoramide	[22224-92-6]	Nemacur fenamiphos	nematicide
/			
isopropylammonium dodecylbenzenesulfonate	[26264-05-1]		dry-cleaning detergent
/			
<i>From Diisopropylamine</i>			
<i>S</i> (2,3-dichloroallyl)- <i>N,N</i> -diisopropylthiocarbamate	[2303-16-4]	Avadex diallate	herbicide
<i>From Diallylamine</i>			
copolymers of dimethyldiallylammonium chloride with acrylates or acrylamides		DMDAC, DADMAC, DADM	water treatment
<i>From Mono-<i>n</i>-butylamine</i>			
di- <i>n</i> -butylthiourea	[32841-23-9]		rubber accelerator
/			
sodium di- <i>n</i> -butylthiocarbamate	[66344-11-4]		rubber accelerator
/			
tetra- <i>n</i> -butylthiuram disulfide	[1634-02-2]	Pentexne	rubber accelerator
zinc di- <i>n</i> -butyldithiocarbamate	[136-23-2]		rubber accelerator
methyl (<i>n</i> -butylcarbamoyl)-2-benzimidazole carbamate	[17804-35-2]	Benlate benomy	fungicide
/			
<i>From Di-<i>n</i>-butylamine</i>			
di- <i>n</i> -butylamine	[111-92-2]		catalyst for polyphenylene ethers
2-(di- <i>n</i> -butylamino)ethanol	[102-81-8]		emulsifier
<i>From Tri-<i>n</i>-butylamine</i>			
tri- <i>n</i> -butylamine	[102-82-9]		urethane catalyst
<i>From Monoisobutylamine</i>			
<i>S</i> -ethyldiisobutyl thiocarbamate	[2008-41-5]	Sutan, Gennate, butylate	herbicide
<i>From Mono-<i>t</i>-butylamine</i>			
<i>N-t</i> -butyl-2-benzothiazole sulfenamide	[95-31-8]	Santocure NS, Delac NS	rubber accelerator
2- <i>t</i> -butylamino-4-ethylamino-6-methyl-thio-1,3,5-triazine	[886-50-0]	Igran	herbicide
3- <i>t</i> -butyl-5-chloro-6-methyluracil	[5902-51-2]	Sinbar	herbicide

Table 5. Manufacturing Data for Aliphatic Amines

Company and plant location	Amine products	Capacity, t yr	Method
<i>United States producers</i>			
Air Products and Chemicals	methyl	68,200	1
	C ₂ –C ₄ + morpholine	63,600	1,2,3
E. I. du Pont de Nemours & Co., Inc.	methyl	81,800	1
Hoechst Celanese	C ₂ –C ₄	36,400 ^a	2,5
Fine Chemicals Division	allyl and methylallyl	3,200	7
Alcolac	methyl	10,000	1
BASF	morpholine	4,500	2
Texaco	morpholine	12,000	2
Atochem North America Elf Aquitaine	C ₂ –C ₅	13,600	2
Sterling Chemicals	<i>t</i> -butyl	5,500	4
Total United States		298,800	
<i>Other American producers</i>			
Chinook Chemicals	methyl	9,000	1
Celanese Mexicana	methyl	8,000	1
BASF Quimica da Bahia	methyl	10,000	1
Nordeste Quimica	C ₂ –C ₄	12,000	1,2
Total U.S. and Americas		320,700	
<i>West European producers</i>			
BASF	methyl	60,000	1
	C ₂ –C ₅	62,000 ^a	1,2
	<i>t</i> -butyl	6,000	6
UCB	methyl	28,000	1
Virchem	C ₃ –C ₅	8,000 ^a	2
ATOCHEM	C ₂ –C ₄	25,000	1,2
Rhône-Poulenc Chimie	<i>n</i> -butyl	2,000	2
Bayer AG	C ₂	8,000	1,2
Ruhrchemie	C ₃ –C	20,000	2
Akzo	methyl	30,000	1
Ertisa	methyl	12,000	1
Imperial Chemical Industries	methyl	33,000	1
	C ₂ –C ₄	12,000	1,2
Total Western Europe		306,000	

	<i>Japanese producers</i>		
Daicel Chemical Industries	C ₂	10,000	1,2
	C ₃	1,000	2
Koei Chemical	C ₃ –C ₄	1,800	2,3
Mitsubishi Gas Chemical	methyl	22,000	1
	C ₂	2,400	3
Nitto Chemical Industry	methyl	23,400	1
	<i>t</i> -butyl	1,500	4
Sumitomo Chemical	<i>t</i> -butyl	1,000	4
<i>Total Japan</i>		<i>63,100</i>	
<i>Total</i>		<i>689,800</i>	

^a Includes cyclohexylamine, see cycloaliphatic amines.

Table 6. Alkylamines Specifications and Economic Data

Compound	Assay, wt %	Other amines, wt %	Water, wt %	1991 U.S. price, \$ /kg
methylamine	99.5	0.3	0.1	1.04
dimethylamine	99.5	0.1	0.1	1.04
trimethylamine	99.5	0.2	0.1	1.04
ethylamine	99.5	0.4	0.1	2.58
diethylamine	99.0	0.7	0.3	2.67
triethylamine	99.5	0.4	0.1	2.76
<i>n</i> -propylamine	99.0	0.5	0.5	2.45
di- <i>n</i> -propylamine	99.0	0.9	0.2	2.69
tri- <i>n</i> -propylamine	98.0	0.6	0.3	3.59
isopropylamine	99.0	0.7	0.3	2.16
diisopropylamine	99.5	0.3	0.2	2.95
<i>n</i> -butylamine	99.5		0.1	2.76
di- <i>n</i> -butylamine	99.0	0.3	0.2	2.89
tri- <i>n</i> -butylamine	98.0	0.6	0.3	3.48
diisobutylamine	98.0	1.3	0.2	2.78
ethyl- <i>n</i> -butylamine	98.5	1.5	0.2	4.39
morpholine	99.0		0.2	2.14

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CYCLOALIPHATIC AMINES

Cycloaliphatic amines are comprised of a cyclic hydrocarbon structural component and an amine functional group external to that ring. Included in an extended cycloaliphatic amine definition are aminomethyl cycloaliphatics. Although some cycloaliphatic amine and diamine products have direct end use applications, their major function is as low cost organic intermediates sold as moderate volume specification products.

Physical Properties

For simple primary amines directly bonded to a cycloalkane by a single C—N bond to a secondary carbon the homologous series is given in Table 1. Up through C₈ each is a colorless liquid at room temperature. The ammoniacal or fishy odor and high degree of water solubility decrease with increased molecular weight and boiling point for these corrosive, hygroscopic mobile fluids.

Table 1. Properties of Primary Aminocycloalkanes

Cycloaliphatic amine	CAS Registry Number	Molecular formula	Boiling point, °C	Flash point, °C	Specific gravity, g/mL	Refractive index, n _D
cyclopropylamine	[765-30-0]	C ₃ H ₇ N	49	26	0.824	1.4210
cyclobutylamine	[2516-34-9]	C ₄ H ₉ N	82	4	0.833	1.4363
cyclopentylamine	[1003-03-8]	C ₅ H ₁₁ N	108	17	0.863	1.4478
cyclohexylamine	[108-91-8]	C ₆ H ₁₃ N	134	32	0.868	1.4565
cycloheptylamine	[5452-35-7]	C ₇ H ₁₅ N	169	42		1.4724
cyclooctylamine	[5452-37-9]	C ₈ H ₁₇ N	190	80	0.928	1.4804
cyclododecylamine	[1502-03-0]	C ₁₂ H ₂₅ N	280 ^a	121		

^a Melting point 27°C.

When additional substituents are bonded to other alicyclic carbons, geometric isomers result. Table 2 lists primary (1°), secondary (2°), and tertiary (3°) amine derivatives of cyclohexane and includes CAS Registry Numbers for cis and trans isomers of the 2-, 3-, and 4-methylcyclohexylamines in addition to identification of the isomer mixtures usually sold commercially. For the 1,2- and 1,3-isomers, the racemic mixture of optical isomers is specified; ultimate identification by CAS Registry Number is listed for the (+) and (-) enantiomers of *trans*-2-methylcyclohexylamine. The 1,4-isomer has a plane of symmetry and hence no chiral centers and no stereoisomers. The methylcyclohexylamine geometric isomers have different physical properties and are interconvertible by dehydrogenation–hydrogenation through the imine.

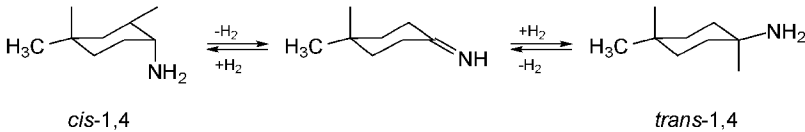


Table 3 lists cycloaliphatic diamines. Specific registry numbers are assigned to the optical isomers of *trans*-1,2-cyclohexanediamine; the cis isomer is achiral at ambient temperatures because of rapid interconversion of ring conformers. Commercial products are most often marketed as geometric isomer mixtures, though large differences in symmetry may lead to such wide variations in physical properties that separations by classical unit operations are practicable, as in Du Pont's fractional crystallization of *trans*-1,4-cyclohexanediamine (mp 72°C) from the low melting (5°C) cis–trans mixture.

Table 2. Properties of Substituted Aminocycloalkanes

Cycloaliphatic amine	CAS Registry Number	Molecular formula	Boiling point, °C	Flash point, °C
1-methylcyclohexylamine	[6526-78-9]	C ₇ H ₁₅ N	140	
2-methylcyclohexylamine	[7003-32-9]	C ₇ H ₁₅ N		22
(±) <i>cis</i> -2-methylcyclohexylamine	[2164-19-4]	C ₇ H ₁₅ N	154	
(±) <i>trans</i> -2-methylcyclo-hexylamine	[931-10-2]	C ₇ H ₁₅ N	150	
(+)- <i>t</i> -2-methylcyclohexylamine	[29569-76-4]	C ₇ H ₁₅ N		
(-)- <i>t</i> -2-methylcyclohexylamine	[931-11-3]	C ₇ H ₁₅ N		
3-methylcyclohexylamine	[6850-35-7]	C ₇ H ₁₅ N		24
(±) <i>cis</i> -3-methylcyclohexylamine	[1193-16-4]	C ₇ H ₁₅ N	153	
	[1193-17-5]	C ₇ H ₁₅ N	152	
(±) <i>trans</i> -3-methylcyclo-hexylamine	[6321-23-9]			
4-methylcyclohexylamine	[17746-6]	C ₇ H ₁₅ N		27
<i>cis</i> -4-methylcyclohexylamine	[2523-56-0]	C ₇ H ₁₅ N	154	
<i>trans</i> -4-methylcyclohexylamine	[2523-55-9]	C ₇ H ₁₅ N	152	
3,3,5-trimethylcyclohexylamine	[15901-42-5]	C ₉ H ₁₉ N	180	60
4- <i>tert</i> -butylcyclohexylamine	[5400-88-4]	C ₁₀ H ₂₁ N	213	79
N-methylcyclohexylamine	[100-60-7]	C ₇ H ₁₅ N	149	30

N-ethylcyclohexylamine	[5459-93-8]	C ₈ H ₁₇ N	165	44
N,N-dimethylcyclohexylamine	[98-94-2]	C ₈ H ₁₇ N	159	42
N,N-diethylcyclohexylamine	[91-65-6]	C ₁₀ H ₂₁ N	194	58
dicyclohexylamine	[101-83-7]	C ₁₂ H ₂₃ N	256	96
N-methyldicyclohexylamine	[7560-83-0]	C ₁₃ H ₂₅ N	265	101
1-adamantylamine	[768-94-5]	C ₁₀ H ₁₇ N	^a	

^a Melting point 207°C.

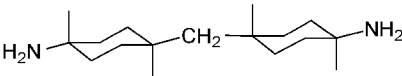
Table 3. Properties of Cycloaliphatic Diamines

Diamine	CAS Registry Number	Molecular formula	Boiling point ^a , °C	Flash point, °C
<i>cis,trans</i> -1,2-cyclohexanediamine	[694-83-7]	C H ₁₄ N ₂	183	75
<i>cis</i> -1,2-cyclohexanediamine	[1436-59-5]	C H ₁₄ N ₂	182	72
(±) <i>trans</i> -1,2-cyclohexanediamine	[1121-22-8]	C H ₁₄ N ₂		
(+) <i>trans</i> -1,2-cyclohexanediamine	[21436-03-3]	C H ₁₄ N ₂		
(-) <i>trans</i> -1,2-cyclohexanediamine	[20439-47-8]	C H ₁₄ N ₂		
<i>cis,trans</i> -1,3-cyclohexanediamine	[3385-21-5]	C H ₁₄ N ₂		91
<i>cis</i> -1,3-cyclohexanediamine	[26772-34-9]	C H ₁₄ N ₂	198	
<i>trans</i> -1,3-cyclohexanediamine	[26883-70-5]	C H ₁₄ N ₂	203	
methylcyclohexanediamine	[28282-16-0]	C ₇ H ₁ N ₂	99 (1.66)	83
<i>cis,trans</i> -1,3-cyclohexanediamine,2-methyl	[13897-56-8]			
<i>cis,trans</i> -1,3-cyclohexanediamine,4-methyl	[13897-55-7]			
<i>cis,trans</i> -1,4-cyclohexanediamine	[1436-59-5]	C H ₁₄ N ₂	181	80
<i>cis</i> -1,4-cyclohexanediamine	[15827-56-2]	C H ₁₄ N ₂		
<i>trans</i> -1,4-cyclohexanediamine	[2615-25-0]	C H ₁₄ N ₂	197	71
<i>cis,trans</i> -1,8-menthanediamine	[80-52-4]	C ₁₀ H ₂₂ N ₂	210	102
<i>cis,trans</i> -1,3-di(aminomethyl)cyclohexane	[2579-20-6]	C ₈ H ₁₈ N ₂		106
<i>cis</i> -1,3-di(aminomethyl)cyclohexane	[10304-00-8]		114 (1.07)	
<i>trans</i> -1,3-di(aminomethyl)cyclohexane	[10339-97-6]		117 (1.33)	
<i>cis,trans</i> -1,4-di(aminomethyl)cyclohexane	[2549-93-1]	C ₈ H ₁₈ N ₂	245	107
<i>cis</i> -1,4-di(aminomethyl)cyclohexane	[10029-09-9]	C ₈ H ₁₈ N ₂		
<i>trans</i> -1,4-di(aminomethyl)cyclohexane	[10029-07-9]			
<i>cis,trans</i> -isophoronediamine	[2855-13-2]	C ₁₀ H ₂₂ N ₂	252	112
methylenedi(cyclohexylamine)	[1761-71-3]	C ₁₃ H ₂ N ₂	162 (2.40)	>110
isopropylidenedi(cyclohexylamine)	[3377-24-0]	C ₁₅ H ₃₀ N ₂	182 (1.32)	>110
3,3'-dimethylmethylene-di(cyclohexylamine)	[6864-37-5]	C ₁₅ H ₃₀ N ₂	160 (0.27)	174
<i>cis,trans</i> -tricyclodecanediamine ^b	[68889-71-4]	C ₁₂ H ₂₂ N ₂	~314	165

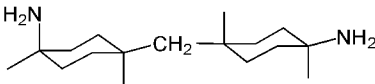
^a At 101.3 kPa unless otherwise indicated by the value (in kPa) in parentheses. To convert kPa to mm Hg, multiply by 7.5.

^b (4,7-Methano-1*H*-indene-dimethaneamine, octahydro).

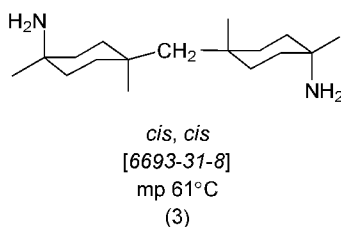
Two-ring cycloaliphatic diamines such as methylenedi(cyclohexylamine) (MDCHA), historically misnamed bis(*para*-amino cyclohexylmethane), or PACM, also exhibit critically dependent fundamental physical properties as a function of configurational isomerism, the simplest and most important being melting point.



trans, trans
[6693-29-4]
mp 65°C
(1)



cis, trans
[6693-30-7]
mp 36°C
(2)



Chemical Properties

Cycloaliphatic amines are strong bases with chemistry similar to that of simpler primary, secondary, or tertiary amines. Upon reaction with nitrous acid, primary amines evolve nitrogen and generate alcohols; secondary amines form mutagenic nitrosamines. Substituted amides are formed under forcing Schotten-Baumann alkaline conditions from primary and secondary amines using acid chlorides; benzamides from benzoyl chloride distinguish 1° and 2° from 3° amines. The Hinsberg test using benzenesulfonyl chloride differentiates water soluble primary amine sulfonamide derivatives from insoluble secondary amine derivatives; tertiary amines are unreactive. Oxidation of secondary carbon primary amines proceeds through hydroxylamine (CH—NHOH) to oxime (C=NOH) and ultimately to the nitroalkane (CH—NO₂). Hydrogen peroxide generates amine oxides from tertiary cycloaliphatic amines.

Salt formation with Brønsted and Lewis acids and exhaustive alkylation to form quaternary ammonium cations are part of the rich derivatization chemistry of these amines. Carbamates and thiocarbamates are formed with CO₂ and CS₂, respectively; the former precipitate from neat amine as carbamate salts but are highly water soluble.

Primary cycloaliphatic amines react with phosgene to form isocyanates. Reaction of isocyanates with primary and secondary amines forms ureas. Dehydration of ureas or dehydrosulfurization of thioureas results in carbodiimides. The nucleophilicity that determines rapid amine reactivity with acid chlorides and isocyanates also promotes epoxide ring opening to form hydroxyalkyl- and dihydroxyalkylamines. Michael addition to acrylonitrile yields stable cyanoethylcycloalkylamines.

Cycloaliphatic diamines react with dicarboxylic acids or their chlorides, dianhydrides, diisocyanates and di- (or poly-)epoxides as comonomers to form high molecular weight polyamides, polyimides, polyureas, and epoxies. Polymer property dependence on diamine structure is greater in the linear amorphous thermoplastic polyamides and elastomeric polyureas than in the highly crosslinked thermoset epoxies (2–4).

Manufacture and Processing

Cycloaliphatic amine synthesis routes may be described as distinct synthetic methods, though practice often combines, or hybridizes, the steps that occur: amination of cycloalkanols, reductive amination of cyclic ketones, ring reduction of cycloalkenylamines, nitrile addition to alicyclic carbocations, reduction of cyanocycloalkanes to aminomethylcycloalkanes, and reduction of nitrocycloalkanes or cyclic ketoximes.

Secondary alcohols are aminated to secondary amines by dehydration catalysts or under H₂ pressure using metal dehydrogenation catalysts such as Ni or Co. The latter process becomes mechanistically equivalent to reductive alkylation of ammonia, though no hydrogen is consumed. Cyclohexylamine (CHA) is commercially produced from cyclohexanol [108-93-0] by reaction in the vapor phase with NH₃ and H₂. Controlled alkyl:ammonia, hydrogen ratios over metal dehydrogenation catalysts on solid supports at 160–200°C and 1350–2000 kPa (196–290 psi) at gas hourly space velocities of 1000–2500 vol vol are analogous conditions to those of the preferred manufacturing process for other secondary aliphatic amines. Reduction of ammonia to cyclohexanol feed ratios in the fixed bed vapor phase process promotes dicyclohexylamine (DCHA) coproduction.

Reductive amination of cyclic ketones, or reductive alkylation of ammonia, is a general route to cycloaliphatic amines (5). Use of pressurized hydrogen and metal catalyst is the process technology of choice commercially; alternative (6) hydrogen sources include formic acid. Batch liquid-phase reaction technology predominates because cyclic ketone volatilization in the presence of ammonia leads to by-product-forming aldol condensations; higher molecular weight alicyclic ketones such as 2-adamantanone [700-58-3] are insufficiently volatile. Short contact time (1–30 s), high temperature (to 275°C), and atmospheric vapor-phase reaction conditions for production of cyclohexylamine from mixtures of cyclohexanol and cyclohexanone [108-94-1] over heated copper chromite–nickel catalyst with an ammonia:alkyl ratio of 3.3:1 and hydrogen:alkyl ratio of 6.5:1 have, however, been claimed (8).

Aniline [62-53-3] ring reduction produces cyclohexylamine. Alternative historical synthetic routes and early (1905–1931) metal-catalyzed hydrogen additions under hydrogen pressure have been well reviewed (9). Increased efficiencies compared to those with Ni and Co catalysts are available from the more precious elements of the same subgroup, Ru and Rh. Batch reaction giving >90% selectivity to CHA with <5% DCHA may use 1–3% of supported precious metal catalyst and neat substrate. Representative reaction conditions are 100–150°C with 1400–3500 kPa (200–500 psi) H₂ requiring 4–20 hours. Subsequent distillation may be batch or continuous. CHA fractionation from trace reaction by-product lights, then from recoverable DCHA and distillate heavies is done under reduced pressure. CHA has been made directly from phenol at low H₂ plus NH₃ pressure using rhodium catalyst in batch reactions (10) and in the vapor phase over nickel (11). Reaction selectivity to CHA is but 56% with 37% DCHA in the latter case.

Reductive amination of cyclohexanone using primary and secondary aliphatic amines provides *N*-alkylated cyclohexylamines. Dehydration to imine for the primary amines, to endocyclic enamine for the secondary amines is usually performed *in situ* prior to hydrogenation in batch processing. Alternatively, reduction of the *N*-alkylanilines may be performed, as for *N,N*-dimethylcyclohexylamine from *N,N*-dimethylaniline [121-69-7] (12,13). One-step routes from phenol and the alkylamine (14) have also been practiced.

Dicyclohexylamine may be selectively generated by reductive alkylation of cyclohexylamine by cyclohexanone (15). Stated batch reaction conditions are specifically 0.05–2.0% Pd or Pt catalyst, which is reusable, pressures of 400–700 kPa (55–100 psi), and temperatures of 75–100°C to give complete reduction in 4 h. Continuous vapor-phase amination selective to dicyclohexylamine is claimed for cyclohexanone (16) or mixed cyclohexanone plus cyclohexanol (17) feeds. Conditions are 5–15 s contact time of <1 : 1 ammonia:ketone, ~3 : 1 hydrogen:ketone at 260°C over nickel on kieselguhr. With mixed feed the preferred conditions over a mixed copper chromite plus nickel catalyst are 18-s contact time at 250 °C with ammonia:alkyl 0.6 : 1 and hydrogen:alkyl 1 : 1.

DCHA is normally obtained in low yields as a coproduct of aniline hydrogenation. The proposed mechanism of secondary amine formation in either reductive amination of cyclohexanone or arene hydrogenation illuminates specific steps (Fig. 1) on which catalyst, solvents, and additives moderating catalyst supports all have effects.

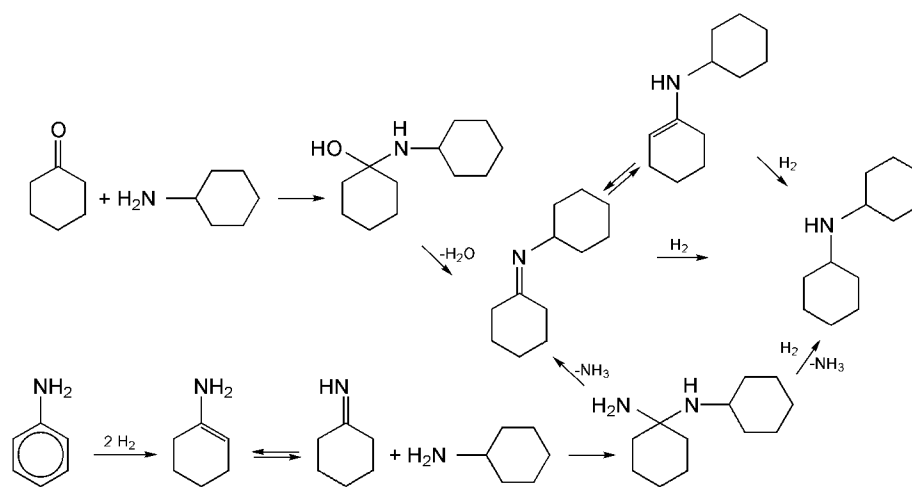
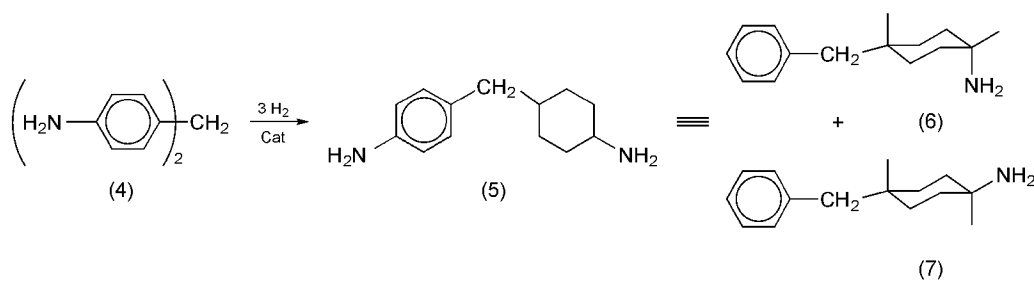


Fig. 1. Routes to dicyclohexylamine (DCHA).

Alkali moderation of supported precious metal catalysts reduces secondary amine formation and generation of ammonia (18). Ammonia in the reaction medium inhibits Rh, but not Ru precious metal catalyst. More secondary amine results from use of more polar protic solvents, $\text{CH}_3\text{OH} > \text{C}_2\text{H}_5\text{OH} > t\text{-C}_4\text{H}_9\text{OH}$. Lithium hydroxide is the most effective alkali promoter (19), reducing secondary amine formation and hydrogenolysis. The general order of catalyst proclivity toward secondary amine formation is $\text{Pt} > \text{Pd} \gg \text{Ru} > \text{Rh}$ (20). Rhodium's catalyst support contribution to secondary amine formation decreases in the order carbon > alumina > barium carbonate > barium sulfate > calcium carbonate.

Methylenedianiline (4) (MDA) [101-77-9] hydrogenation to methylenedi(cyclohexylamine) generates first the *cis*-(6) and *trans*-(7) isomers of half-reduced 4-(*p*-aminobenzyl)-cyclohexylamine (5) [28480-77-5], a differentially reactive diamine offered in developmental quantities by Air Products and Chemicals.

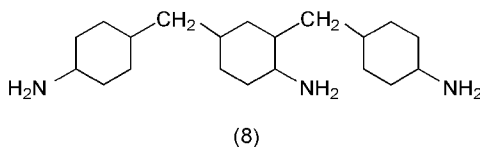


Addition of H_2 to the aromatic ring occurs *cis*, yielding a kinetic product subject to isomerization to the more thermodynamically stable *trans* isomer.

Subsequent hydrogen addition to the remaining aromatic ring then produces the three fully reduced isomers (1–3). Catalyst systems were first optimized for efficient maximum *trans* isomer production (21–23). Batch reaction conditions using Ru on alumina catalyst for obtaining the thermodynamic mixture of product isomers were 200°C and 28–35 MPa (4000–5000 psi). Improved yields, including isomerization to a 50 : 40 : 10 mixture of (1,2,3), are enhanced by Ru alkali moderation (13,24,25).

Conditions cited for Rh on alumina hydrogenation of MDA are much less severe, 117°C and 760 kPa (110 psi) (26). With 550 kPa (80 psi) ammonia partial pressure present in the hydrogenation of twice-distilled MDA employing 2-propanol solvent at 121°C and 1.3 MPa (190 psi) total pressure, the supported Rh catalyst could be extensively reused (27). Medium pressure (3.9 MPa = 566 psi) and temperature (80°C) hydrogenation using iridium yields low *trans/trans* isomer MDCHA (28). Improved selectivity to alicyclic diamine from MDA has been claimed (29) for alumina-supported iridium and rhodium by introducing the tertiary amines 1,4-diazabicyclo[2.2.2]octane [280-57-9] and quinuclidine [100-76-5].

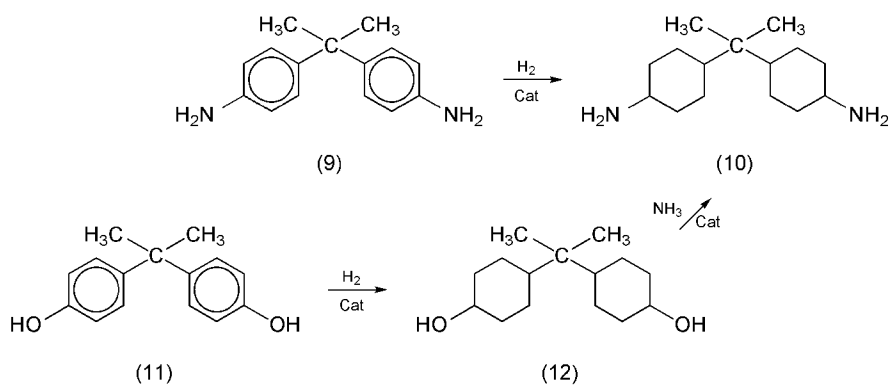
Direct production of select MDCHA isomer mixtures has been accomplished using ruthenium dioxide (30), ruthenium on alumina (31), alkali-moderated ruthenium (32) and rhodium (33). Specific isomer mixtures are commercially available from an improved 5–7 MPa (700–1000 psi) medium pressure process tolerant of oligomer-containing MDA feeds (34). Dimethylenetri(cyclohexylamine) (8) [25131-42-4] is a coproduct.



Continuous solvent-free hydrogenation of MDA over alkaline-earth-supported metals at 240°C and 25 MPa (3600 psi) has been described (35) as well as a similar high pressure process employing diluent solvent (36). MDA with isomeric impurities and oligomeric contaminants has been hydrogenated in a continuous flow system to advantage by first pretreating with Ni catalyst (150°C), then sequentially performing Ru hydrogenation at 185–200°C and 18 MPa (2600 psi) (37) (see also AMINES, AROMATIC, METHYLENEDIANILINE).

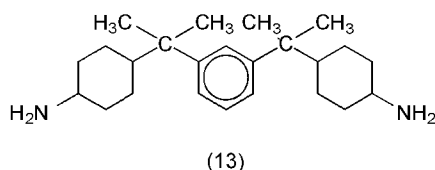
Batch syntheses comparable to those used for MDA produce 3,3'-dimethylmethylenedi(cyclohexylamine) marketed under the trade name Laromin C-260. The starting aromatic diamine, 3,3'-dimethylmethylenedianiline [838-88-0], is prepared from *o*-toluidine [95-53-4] condensation with formaldehyde. Similarly 3,3'-dimethyldicyclohexylamine [24066-10-2] may be produced (38) from *o*-toluidine [119-93-7] derived from *o*-nitrotoluene [88-72-2]. The resultant isomer mixtures are dependent on reduction conditions as in MDA hydrogenation.

Isopropylidenedi(cyclohexylamine) (PDCHA) (10) may be made by precious metal hydrogenation of isopropylidenedianiline (9) [2479-47-2], the condensation product of acetone [67-64-1] and aniline, commonly termed bisaniline A. A number of metal catalysts have been shown effective in an alternative route, the amination of isopropylidenedi(cyclohexanol) (12) [80-04-6] (39,40), the ring reduction product of bisphenol A (11) [80-05-7]. Ruthenium has been used for both the bisphenol ring reduction (210°C, 24 MPa H_2 = 3500 psi) and then a subsequent amination following ammonia addition. Batch amination of the cycloaliphatic diol (12) over a Co–Mn phosphoric acid-modified catalyst is only accomplished by initially pressurizing to 5 MPa (700 psi) with H_2 , then adding NH_3 to a new autoclave pressure of 30 MPa (4350 psi) at 170°C, removing the water of reaction by venting, and cycling H_2 and NH_3 anew.

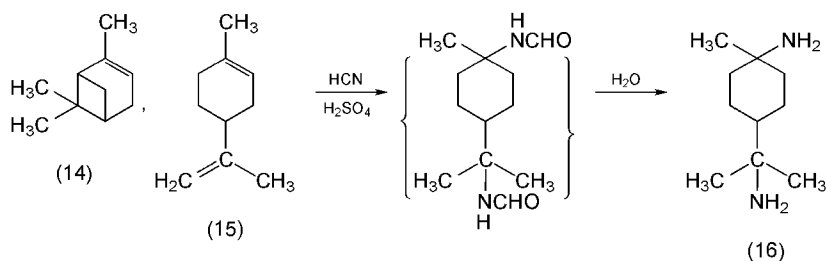


Trickle bed reaction of diol (12) using amine solvents (41) has been found effective for producing PDCHA, and heavy hydrocarbon codistillation may be used to enhance diamine purification from contaminant monoamines (42). Continuous flow amination of the cycloaliphatic diol in a liquid ammonia mixed feed gives >90% yields of cycloaliphatic diamine over reduced Co Ni Cu catalyst on phosphoric acid-treated alumina at 220°C with H_2 to yield a system pressure of 30 MPa (4350 psi) (43).

Cycloaliphatic diamines such as (13) [115172-12-8] which retain some aromatic character have been made from end-ring hydrogenation (44) of 1,3-bis(*p*-aminocumyl)benzene [2687-27-6], the double alkylation adduct of aniline to *m*-diisopropenylbenzene [3748-13-8] (45) using Ru catalysts (46).

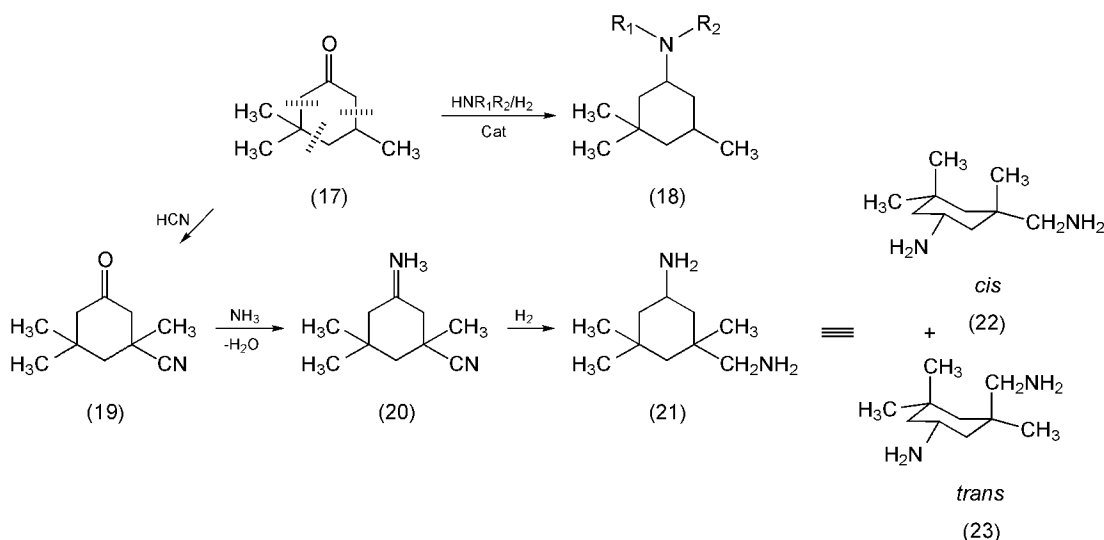


Cycloaliphatics capable of tertiary carbocation formation are candidates for nucleophilic addition of nitriles. HCN in strong sulfuric acid transforms 1-methyl-1-cyclohexanol to 1-methyl-1-cyclohexylamine through the formamide (47). The terpenes pinene (14) [2437-95-8] and limonene [5989-27-5] (15) each undergo a double addition of HCN to provide, after hydrolysis, the cycloaliphatic diamine 1,8-menthenediamine (16) (48).



1-Adamantylamine is prepared from the corresponding alcohol or bromide by bridgehead cation generation in the presence of acetonitrile (49). Selective hydrolysis of the resultant acetamide to the rigid cycloaliphatic amine by acid or base is difficult.

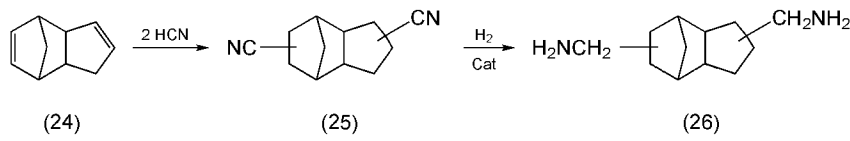
Acetone's cyclic trimer, isophorone (17) [78-59-1], has reacted directly with ammonia (Ra Ni, 120°C), methylamine (Pt C, 100°C) and dimethylamine (Pd C, 95°C) at 2400–3450 kPa H_2 pressure to form 3,3,5-trimethylcyclohexylamines (18), where $R_1, R_2 = H, \text{ alkyl}$ (50). The double bond is hydrogenated simultaneously with the imine:



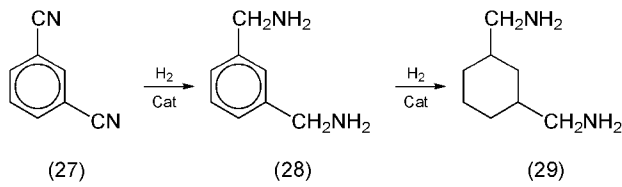
3-Aminomethyl-3,5,5-trimethylcyclohexylamine (21), commonly called isophoronediamine (IPD) (51), is made by hydrocyanation of (17) (52), (53) followed by transformation of the ketone (19) to an imine (20) by dehydrative condensation of ammonia (54), then concomitant hydrogenation of the imine and nitrile functions at 15–16 MPa (~2200 psi) system pressure and 120°C using methanol diluent in addition to H_2 and NH_3 . Integrated imine formation and nitrile reduction by reductive amination of the ketone leads to alcohol by-product. There are two geometric isomers of IPD; the major product is *cis*-(22) [71954-30-5] and the minor, *trans*-(23) [71954-29-5] (55).

1,2-Cyclohexanediamine's commercial origin is its presence as a minor 0.1–<1% coproduct of hexamethylenediamine [124-09-4] produced by hydrogenation of adiponitrile [111-69-3]. Fractional distillation by up to four columns in a series is routine commercial practice to purify nylon grade acyclic diamine; the crude cycloaliphatic diamine requires further refining before use as a specification intermediate.

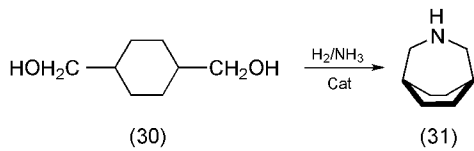
Dicyclopentadiene (24) [77-73-6] is an inexpensive raw material for hydrocyanation to (25), a mixture of 1,5-dicarbonitrile [70874-28-1] and 2,5-dicarbonitrile [70874-29-2], then subsequent hydrogenation to produce tricyclodecanediamine, TCD diamine (26). This developmental product, a mixture of endo and exo, *cis* and *trans* isomers, is offered by Hoechst.



Di(aminomethyl)cyclohexanes are potentially available from large volume starting materials. The 1,3-isomer (29) may be produced by reduction of *m*-xylylenediamine (28) [1477-55-0] or directly upon exhaustive hydrogenation of isophthalonitrile (27) [626-17-5].



The 1,4-isomer has been similarly generated from terephthalonitrile [623-26-7] (56) using a mixed Pd Ru catalyst and ammonia plus solvent at 125°C and 10 MPa (100 atm). It is also potentially derived (57) from terephthalic acid [100-21-0] by amination of 1,4-cyclohexanedimethanol (30) [105-08-8]. Endocyclization, however, competes favorably and results in formation of the secondary amine (31) 3-azabicyclo[3.2.2]nonane [283-24-9] upon diol reaction with ammonia over dehydration and dehydrogenation catalysts (58):



Production and Shipment

Larger volume cycloaliphatic amines and diamines, their worldwide major manufacturers and approximate January 1990 prices are shown in Table 4. Shipment of these liquid products is by nitrogen-blanketed tank truck or tank car. Drum shipments are usually in carbon steel, DOT-17E.

Table 4. Commercial Cycloaliphatic Amines

Amine	Volume, 10 ³ t yr	Price, \$ kg	Manufacturers
cyclohexylamine	20	2.90	Air Products, BASF, Bayer, Hoechst, ICI, Kanto Denka, New Japan
isophoronediamine	18	5.40	HbIs
methylenedi(cyclohexyl-amine)	10	6.80	Air Products, BASF, HbIs, New Japan
3,3'-dimethylmethylene-di(cyclohexylamine)	3	8.90	BASF
dicyclohexylamine	2	3.75	Air Products, BASF, Hoechst
dimethylcyclohexylamine	2	4.85	Air Products, BASF, ICI
1,2-cyclohexanediamine	1	3.65	Du Pont Milliken

Economic Aspects

Cycloaliphatic amine production economics are dominated by raw material charges and process equipment capital costs. Acetone (isophorone), adiponitrile, aniline, and MDA are all large-volume specification organic intermediates bordering on commodity chemicals. They are each cost-effective precursors.

Reductive alkylations and aminations require pressure-rated reaction vessels and fully contained and blanketed support equipment. Nitrile hydrogenations are similar in their requirements. Arylamine hydrogenations have historically required very high pressure vessel materials of construction. A nominal breakpoint of 8 MPa (~1200 psi) requires yet heavier wall construction and correspondingly more expensive hydrogen pressurization. Heat transfer must be adequate, for the heat of reaction in arylamine ring reduction is ~50 kJ mol (12 kcal mol) (59). Solvents employed to maintain catalyst activity and improve heat-transfer efficiency reduce effective hydrogen partial pressures and require fractionation from product and recycle to prove cost-effective.

Production of cyclohexylamine reflects this balance of raw material versus operating cost structure. When aniline cost and availability are reasonable, the preferred route is aniline ring reduction; alternatively the cyclohexanol amination route is chosen.

Rhodium was about three times the price of gold through 1988–1989 until skyrocketing to \$74 g (~\$2300 troy oz) in early 1990. Thus precious metal catalyst costs require an absolute minimum level of use and maximum number of catalyst recycle uses when batch processing is employed. Starting material contaminants may effect catalyst poisoning, though process routes to overcome this by feed stream pretreatment may be devised (37,60).

Specifications, Standards and Quality Control

Liquid cycloaliphatic amines and diamines have exacting purity and color standards. Almost all are sold to specification, not performance standards. Use as isocyanate precursors requires low water content criteria for these hygroscopic fluids, hence nitrogen blanketing is often specified for product sampling as well as storage and transport.

Contaminant by-products depend upon process routes to the product, so maximum impurity specifications may vary, eg, for CHA produced by aniline hydrogenation versus that made by cyclohexanol amination. Capillary column chromatography has improved resolution and quantitation of contaminants beyond the more fully described packed column methods (61) used historically to define specification standards. Wet chemical titrimetry for water by Karl Fisher or amine number by acid titration have changed little except for their automation. Colorimetric methods remain based on APHA standards.

Analytical and Test Methods, Storage

Isomer separation beyond physical fractional crystallization has been accomplished by derivatization using methyl formate to make *N*-formyl derivatives and acetic anhydride to prepare the corresponding acetamides (1). Alkaline hydrolysis regenerates the analytically pure amine configurational isomers.

Amine chromatographic analyses suffer poor resolution in many gas-liquid column separations because of strong interactions of the basic

functional group and surface active components of even glass column supports. Tailing results. For close-eluting isomers, the problem is magnified. Derivatization of isomeric cycloaliphatic diamines has been reported using *N,N'*-trifluoroacetyl derivatives from reaction with trifluoroacetic anhydride (62). *N,N,N',N'*-Tetramethyl derivatives from formaldehyde–formic acid methylation, the Eschweiler–Clarke procedural variant of the Leuckart reaction (63), avoid amide hydrogen bonding column interactions (64). A more efficient procedure has been detailed for *N,N*-dimethylformamide dimethyacetal reaction with methylene- and isopropylidenedi(cyclohexylamine) geometric isomers to form chromatographically resolvable *N*-dimethylaminomethylene derivatives (65). Improved capillary column technology allows geometric isomer resolution directly, without derivatization (34).

Wet chemical methods determining titratable amine are reported for products entering urethane (amine number as meq g) or epoxy (AHEW = amine hydrogen equivalent weight) trade applications. For secondary amines *N*-nitrosamine contaminants are reportable down to ppb using Thermoelectron Corporation thermal energy analyzer techniques.

Health and Safety Factors (Toxicology)

Cycloaliphatic amines and diamines are extreme lung, skin, and eye irritants. MSD sheets universally carry severe personal protective equipment use warnings due to the risk of irreversible eye damage. These compounds are generally not mutagenic in the Ames test, and are highly (50–500 mg kg) to moderately (500–5000 mg kg) toxic as graded by the Hodge–Sterner scale by acute animal testing (66) (Table 5).

Table 5. Acute Toxicity of Cycloaliphatic Amines

Cycloaliphatic amine	Rat oral LD ₅₀ ^a , mg kg
cyclohexylamine	360
dicyclohexylamine	370
<i>N</i> -methylcyclohexylamine	400
dimethylcyclohexylamine	348
<i>N</i> -ethylcyclohexylamine	590
<i>cis,trans</i> -1,3-cyclohexanediamine	390
methyl-1,3-cyclohexanediamine	1060
4-methyl-1,3-cyclohexanediamine	1410 ^a
1,3-diaminomethylcyclohexane	880
1,4-diaminomethylcyclohexane	530
1,8-menthanediamine	700
1-adamantylamine	900
methylenedi(cyclohexylamine)	450
3,3'-dimethylmethylenedi(cyclohexylamine)	550
tricyclodecanediamine	502

^a Ref. 67.

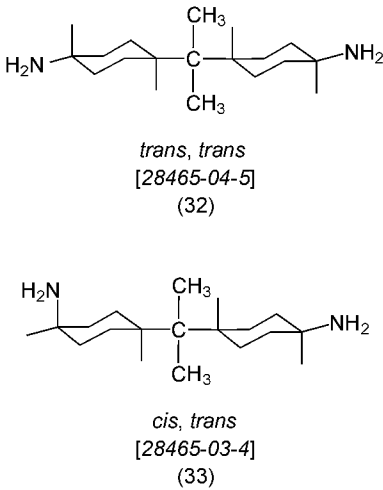
Use of dry chemical, alcohol foam, or carbon dioxide is recommended for cycloaliphatic amine fire fighting. Water spray is recommended only to flush spills away to prevent exposures. In the aquatic environment, cyclohexylamine has a high (420 mg L) toxicity threshold for bacteria (*Pseudomonas putida*) (68), and is considered biodegradable, that is, mineralizable to CO₂ and H₂O, by acclimatized bacteria.

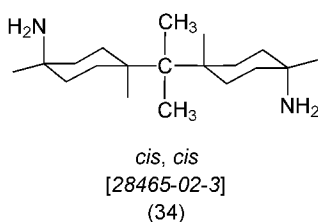
Uses

Cyclohexylamine is miscible with water, with which it forms an azeotrope (55.8° H₂O) at 96.4°C, making it especially suitable for low pressure steam systems in which it acts as a protective film-former in addition to being a neutralizing amine. Nearly two-thirds of 1989 U.S. production of 5000–6000 t yr cyclohexylamine serviced this application (69). Carbon dioxide corrosion is inhibited by deposition of nonwetttable film on metal (70). In high pressure systems CHA is chemically more stable than morpholine [110-91-8] (71). A primary amine, CHA does not directly generate nitrosamine upon nitrite exposure as does morpholine. CHA is used for corrosion inhibitor radiator alcohol solutions, also in paper- and metal-coating industries for moisture and oxidation protection.

Monofunctional, cyclohexylamine is used as a polyamide polymerization chain terminator to control polymer molecular weight. 3,3,5-Trimethylcyclohexylamines are useful fuel additives, corrosion inhibitors, and biocides (50). Dicyclohexylamine has direct uses as a solvent for cephalosporin antibiotic production, as a corrosion inhibitor, and as a fuel oil additive, in addition to serving as an organic intermediate. Cycloaliphatic tertiary amines are used as urethane catalysts (72). Dimethylcyclohexylamine (DMCHA) is marketed by Air Products as POLYCAT 8 for pour-in-place rigid insulating foam. Methylcyclohexylamine is POLYCAT 12 used for flexible slabstock and molded foam. DMCHA is also sold as a fuel oil additive, which acts as an antioxidant. Sterically hindered secondary cycloaliphatic amines, specifically dicyclohexylamine, effectively catalyze polycarbonate polymerization (73).

Cycloaliphatic diamines which have reacted with diacids to form polyamides generate performance polymers whose physical properties are dependent on the diamine geometric isomers. (58,74). Proprietary transparent thermoplastic polyadipamides have been optimized by selecting the proper mixtures of PDCHA geometric isomers (32–34) for incorporation (75):



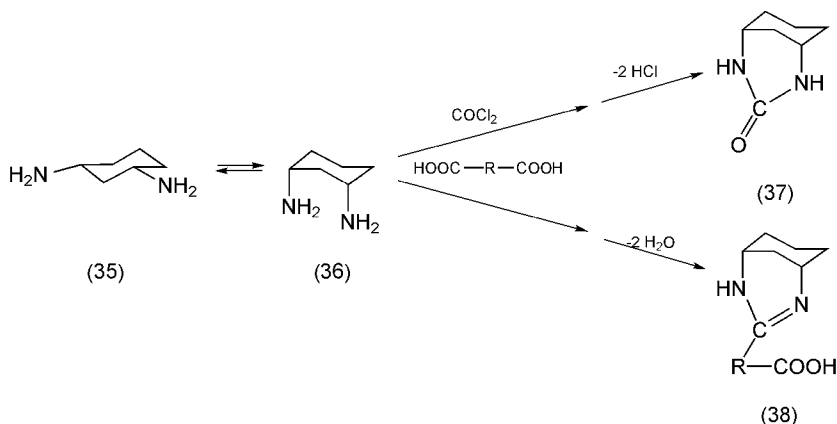


The polyamide copolymer of dodecanoic acid with methylenedi(cyclohexylamine) (MDCHA, PACM) was sold as continuous filament yarn fiber under the tradename QIANA. As late as 1981, over 145,000 t was produced using high percentages, typically 80%, of *trans, trans* MDCHA isomer. The low melting raffinate coproduct left after t,t isomer separation by fractional crystallization was phosgenated to produce a liquid aliphatic diisocyanate marketed by Du Pont as Hylene W. Upon termination of their QIANA commitment, Du Pont sold the urethane intermediate product rights to Mobay, who now markets the 20% *trans*, *trans*–50% *cis*, *trans*–30% *cis*, *cis* diisocyanate isomer mixture as Desmodur W. In addition to its use in polyamides and as an isocyanate precursor, methylenedi(cyclohexylamine) is used directly as an epoxy curative. The liquid diamine mixture identified historically as PACM-20 is marketed as AMICURE PACM by Anchor Chemical for performance epoxies.

1,2-Cyclohexanediamine is marketed by Milliken Chemical as an epoxy curative, Millamine 5260. It may be adducted with epichlorohydrin to generate solventless low viscosity curatives for varnishes and surface coatings (76). Other cycloaliphatic diamines have long been modified as epoxy curatives to modify their reactivity profile (77).

MCHD from ring reduction of TDA (60,78) has been cited as an epoxy curative (79) and is available from Air Products and Chemicals as a developmental cycloaliphatic diamine. Ring reduction of sterically hindered arylendiamines such as diethyltoluenediamine [68479-98-1] provides slower-reacting alkylated 1,3-cyclohexanediamines for polyurethane, polyurea, and epoxy use (80).

Use of 1,3-cycloaliphatic diamines as organic intermediates appears limited because of *cis* isomer endocyclization reactions. Ring hydrogenation of the low cost 80/20 2,4-toluenediamine/2,6-toluenediamine isomer mixture results in 4 geometric isomers of 4-methyl-1,3-cyclohexanediamine, 3 isomers of 2-methyl-1,3-cyclohexanediamine; the overall sum of methyl *cis*-1,3-diamine is ~50%. Phosgenation of the free-base or dicarbamate of hydrogenated TDA to produce methylcyclohexanediiisocyanate results in low yields (81,82), possibly because of endocyclic urea formation. Diequatorial 1,3-cyclohexanediamine (35) is conformationally labile, and in the alternative 1,3-diaxial diamine conformation (36) allows facile condensation to urea (37). Phosgenation of the methylcyclohexanediamine dihydrochloride, however, is efficient, giving ~90% yields of methylcyclohexanediiisocyanate in 4–14 hours at 125–185°C and, depending on solvent, pressure to 1 MPa (145 psi) (83).

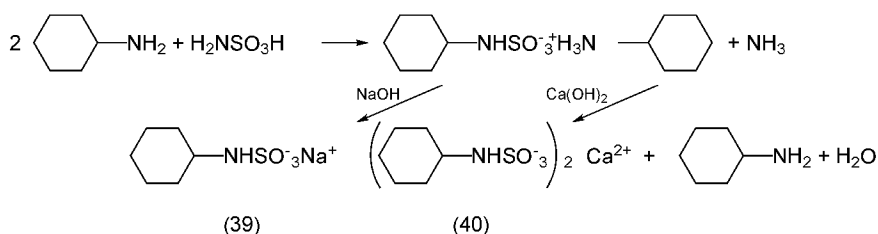


Use of 1,3-cycloaliphatic diamines in polyamides may be similarly limited by internal amide dehydration of the conformationally labile *cis* isomers to form a tetrahydropyrimidine (38) rather than high molecular weight polyamide. 1,3-Cyclohexanediamine is, however, a component of Spandex polyureas; Du Pont uses the hydrogenation product of *m*-phenylenediamine [108-45-2] (24) captively to produce Lycra (see FIBERS, ELASTOMERIC).

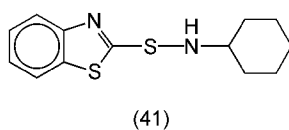
1,8-Menthanediamine has been effectively reacted to form polyamides (84) and is sold in metric tons per year volume as a premium (~\$13/kg) epoxy curative (85) by Rohm and Haas. 1-Adamantylamine hydrochloride [665-66-7] is a prophylactic against type A viral infections sold by Du Pont under the trade name Symmetrel.

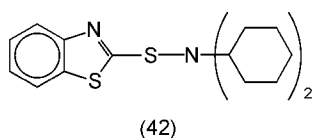
Derivatives

Before a 1/1/70 FDA ban (rescission proposed in early 1990), cyclamate noncaloric sweeteners were the major derivatives driving cyclohexylamine production. The cyclohexylsulfamic acid sodium salt (39) [139-05-9] and more thermally stable calcium cyclohexylsulfamic acid (40) [139-06-1] salts were prepared from high purity cyclohexylamine by, among other routes, a reaction cycle with sulfamic acid.



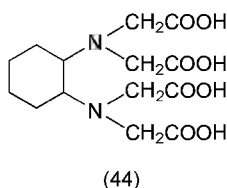
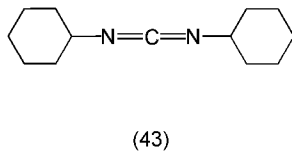
Cyclohexylamine condensed with mercaptobenzothiazole produces the large volume moderated rubber accelerator *N*-cyclohexyl-2-benzothiazolesulfenamide (41) [95-33-0] (see RUBBER COMPOUNDING). DCHA similarly is used in preparing *N,N*-dicyclohexyl-2-benzothiazolesulfenamide (42) [4979-32-2]. The cyclohexylamine derivative is preferred over *tert*-butylamine [75-64-9] and morpholine sulfenamide analogues because of lower amine volatility and less nitrosamine risk respectively.





1,3-Dicyclohexylcarbodiimide (43) [538-75-0] is an important peptide-condensing agent and analytical reagent (86).

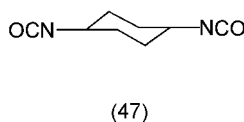
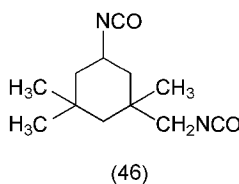
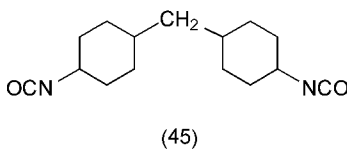
trans-1,2-Cyclohexanediamine is derivatized by Mannich reaction of formaldehyde and HCN, then hydrolyzed to the tetraacetate (44) [13291-61-7] and sold as a chelating agent by the Eastman Kodak and Takeda companies.



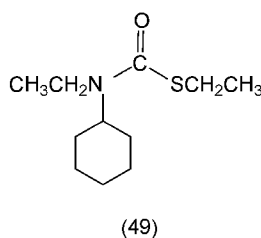
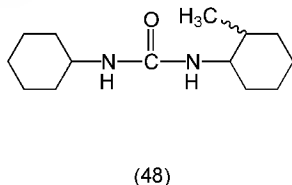
Methylenedi(cyclohexylisocyanate) (45) [5124-30-1] (MDCHI, Desmodur W) is the dominant derivative of MDCHA and is used in light-stable urethanes. Polyurethane physical properties are dependent on the diamine geometric isomer composition used for the derivative diisocyanate which reacts with diol (87).

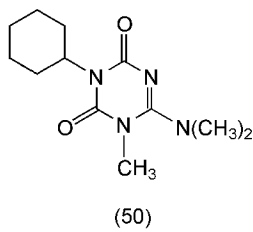
Isophoronediiisocyanate (46) [4098-71-9] made by phosgenation of IPD (88) competes effectively in this same polyurethane market, predominantly coatings, and is the major commercial application of isophoronediamine.

1,4-Cyclohexanediamine from hydrogenation of *p*-phenylenediamine [106-50-3] may be easily phosgenated, unlike the corresponding 1,2- and 1,3-isomers to produce a useful (89) diisocyanate for performance polyurethanes efficiently (90), particularly *trans*-1,4-cyclohexanediisocyanate [2556-36-47] (47) (CHDI). This diamine organic intermediate use competes with an Akzo route to *t*-CHDI from the corresponding diacid without intermediacy of the diamine.



A representative agrochemical application of cycloaliphatic amines is the reaction of the commercial 30/70 *cis*/*trans* isomer mixture of 2-methylcyclohexylamine with phenylisocyanate to give the crabgrass and weed control agent Siduron (1-(2-methylcyclohexyl)-3-phenylurea (48) [1982-49-6] (91). The preplant herbicide Cycloate used for sugar beets, vegetable beets, and spinach, (*S*-ethyl-*N*-ethyl-*N*-cyclohexylthiocarbamate (49) [1134-23-2], incorporates *N*-ethylcyclohexylamine. The herbicide Hexazinone, (3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4-dione (50) [51235-04-2]) is prepared from cyclohexylisocyanate [3173-53-3] (92).





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FATTY AMINES

Fatty amines are nitrogen derivatives of fatty acids, olefins, or alcohols prepared from natural sources, fats and oils, or petrochemical raw materials. Commercially available fatty amines consist of either a mixture of carbon chains or a specific chain length from C₈–C₂₂. The amines are classified as primary, secondary, or tertiary depending on the number of hydrogen atoms of an ammonia molecule replaced by fatty alkyl or methyl groups (Fig. 1). The amino nitrogen is most frequently found on a primary carbon atom, but secondary and tertiary carbon substitution derivatives have been made and are commercially available. Fatty amines are cationic surface-active compounds (see SURFACTANTS), which strongly adhere to surfaces by either physical or chemical bonding, thus modifying surface properties. Important commercial products are prepared using fatty amines as reactive intermediates.

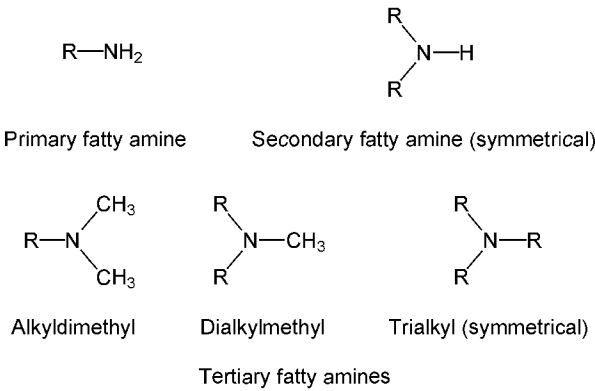


Fig. 1. Types of commercially available fatty amines. R = C₈–C₂₂.

Commercially available fatty amines are most frequently prepared from naturally occurring materials (see FATS AND FATTY OILS) by hydrogenation of a fatty nitrile intermediate using a variety of catalysts (1–3). Naturally occurring fats and oils (triglycerides) are continuously hydrolyzed at 200–280°C to yield saturated and unsaturated fatty acids and glycerol. Fatty nitriles are prepared from fatty acid mixtures by batch or continuous processes. The alkyl chain-length composition of the amines varies depending on the type of fat or oil. Other factors influencing alkyl chain composition include location of source, time of harvest, and, more recently, hybridization. Typical compositions for various fats and oils used to prepare commercially available fatty amines are given in Table 1 (4–8).

Table 1. Typical Fatty Acid Composition

Fatty acid ^a , %	Fat			Fatty oils	
	Tallow	Coconut	Soya	Palm kernel	Palm
caproic (C6:0)		1.2		<0.5	
caprylic (C8:0)		3.4–15.0		2.4–6.2	
capric (C10:0)		3.2–15.0		2.6–6.2	
lauric (C12:0)		41–56		41–55	
myristic (C14:0)	3.0	13–23	0.9	14–20	1
palmitic (C16:0)	29.2	4.2–12.0	7–12	6.5–11.0	43.5
stearic (C18:0)	19.1	1.0–4.7	2.0–5.5	1.3–3.5	4.5
oleic (C18:1)	43.6	3.4–12.0	20–50	10–23	40
linoleic (C18:2)	2.1	0.9–3.7	35–60	0.7–5.4	
linolenic (C18:3)	0.5		2–13		
other	2.5				11

^a The number of carbon atoms and number of double bonds are designated in parentheses.

Fatty amines derived from fats and oils, containing several carbon-chain-length moieties, are designated as such by common names which describe these mixtures: tallowalkylamines [61790-33-8], cocoalkylamines [61788-46-3], and soyaalkylamines [61970-18-9], for example. High purity fatty amines are also commercially available. These amines are prepared by distillation of either the precursor fatty acid or amine product mixture. There are common names for single chain-length fatty amines in addition to IUPAC nomenclature, which uses the alkyl chain length in naming the amine. Secondary and tertiary amines have been named as primary amine derivatives, for example, *N*-hexadecyl-1-hexadecylamine instead of di-*n*-hexadecylamine (IUPAC). Examples include:

Common name	IUPAC name	Molecular formula	CAS Registry Number
laurylamine	1-dodecylamine	C ₁₂ H ₂₇ N	[124-22-1]
palmitylamine	1-hexadecylamine	C ₁₆ H ₃₅ N	[143-27-1]
stearylamine	1-octadecylamine	C ₁₈ H ₃₉ N	[124-30-1]
oleylamine	1-octadecen-9-ylamine	C ₁₈ H ₃₇ N ^(unsaturated)	[112-90-3]

Trade names are commonly used for commercial products.

In recent years, especially in the USSR and Europe, synthetic fatty acids, prepared via hydrocarbon oxidation, have been used to prepare fatty amines (2,9). In 1978 Eastern Europeans produced an estimated 0.55 billion kg of synthetic fatty acids with odd and even numbers of carbon atoms, whereas in the United States, production of natural fatty acids with even carbon atom chain-length acids was 435 million kg. To date, there has been no significant production of synthetic fatty acids in the United States.

Fatty alcohols, prepared from fatty acids or via petrochemical processes, aldol or hydroformylation reactions, or the Ziegler process, react with ammonia or a primary or secondary amine in the presence of a catalyst to form amines (10–12).

In addition to the nitrile and alcohol routes just described, many other methods of preparation of fatty amines are available. Some commercially available tertiary fatty amines are prepared via a petrochemical route (13). The amines have been prepared by reaction of an olefin with ammonia or a primary or secondary amine in the presence of a catalyst prepared from a Group 8–10 metal or an ammonium halide (14–16). Nitration of paraffins having from 6 to 30 carbon atoms with nitrogen dioxide at elevated temperatures followed by hydrogenation in the presence of a nickel or palladium catalyst produces secondary alkyl primary amines (17–20). Long-chain, unbranched, aliphatic tertiary amines can be prepared by reaction of an alkyl chloride with an alkyl secondary amine at 100–250°C (21,22). Other methods of producing amines include reaction of a carboxylic acid ester with a secondary amine in the presence of hydrogen at high pressure using a metal oxide catalyst, zinc oxide–chromium oxide or zinc oxide–aluminum oxide (23), or by catalytic hydroammonolysis of carboxylic acids at high pressure and temperature in the presence of a mixture of sulfides of metals of Groups 6 and 8–10 (24). The Hofmann rearrangement, preparation of an amine from an unsubstituted amide using solutions of chlorine in sodium hydroxide, has been useful in preparing long-chain primary amines (25). Amines prepared using the Hofmann rearrangement contain one less carbon atom than the amide. Thus, odd-chain-length fatty amines, not available from natural sources, can be prepared. The Ritter reaction of olefins with hydrogen cyanide in the presence of a strong acid, after hydrolysis, produces tertiary-alkyl primary amines. Rohm and Haas Primene amines are prepared using the Ritter reaction.

Physical Properties

Data on physical properties of fatty amines have been well documented and summarized in many reference works on fatty acids and nitrogen derivatives (3,8,13,26–29). Table 2 lists melting point data of some commercially available primary, secondary, and tertiary fatty amines, and it is evident that: (1) melting points within a homologous series of single-chain-length fatty amines increase with molecular weight, (2) symmetrical secondary amines have a higher melting point than the primary amine of the same alkyl group, but are lower melting than a primary amine with the same number of carbon atoms (hydrogen bonding), (3) symmetrical tertiary amines are lower melting than a symmetrical secondary amine of the same alkyl group, (4) symmetrical tertiary amines are lower melting than a primary or secondary amine containing the same number of carbon atoms, and (5) unsaturation lowers the melting point of the fatty amine, eg, oleylamine versus 1-octadecylamine and ditallowalkylamines versus dihydrogenated tallowalkylamines.

Table 2. Melting Points of Fatty Amines

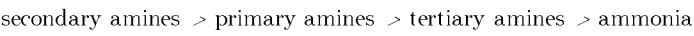
Amine	Molecular formula	CAS Registry Number	Mp, °C
Primary amines			
cocoalkylamines		[61788-46-3]	16.0
1-dodecylamine	C ₁₂ H ₂₇ N	[124-22-1]	28.0
1-hexadecylamine	C ₁ H ₃₅ N	[143-27-1]	46.2
1-octadecylamine	C ₁₈ H ₃₉ N	[124-30-1]	53.0
oleylamine	C ₁₈ H ₃₇ N	[112-90-3]	21.0
soyaalkylamines		[61970-18-9]	29.0
tallowalkylamines		[61790-33-8]	40.0
hydrogenated tallowalkylamines		[61788-45-2]	55.0
Secondary amines			
dicocoalkylamines		[61789-76-2]	43.0
di- <i>n</i> -dodecylamine	C ₂₄ H ₅₁ N	[3007-31-6]	47.0
di- <i>n</i> -hexadecylamine	C ₃₂ H ₇ N	[16724-63-3]	67.0
di- <i>n</i> -octadecylamine	C ₃ H ₇₅ N	[112-99-2]	72.3
ditallowalkylamines		[68783-24-4]	55.0
dihydrogenated tallowalkylamines		[61789-79-5]	62
Tertiary amines			
Alkyldimethyl			
cocoalkyldimethylamines		[61788-93-0]	22
dimethyl- <i>n</i> -octylamine	C ₁₀ H ₂₃ N	[7378-99-6]	57
dimethyl- <i>n</i> -decylamine	C ₁₂ H ₂₇ N	[1120-24-7]	35
dimethyl- <i>n</i> -dodecylamine	C ₁₄ H ₃₁ N	[112-18-5]	15
dimethyl- <i>n</i> -tetradecylamine	C ₁ H ₃₅ N	[112-75-4]	6
dimethyl- <i>n</i> -hexadecylamine	C ₁₈ H ₃₉ N	[112-69-6]	8
dimethyl- <i>n</i> -octadecylamine	C ₂₀ H ₄₃ N	[124-28-7]	21
dimethyloleylamine	C ₂₀ H ₄₁ N	[28061-69-0]	10
Dialkylmethyl			
di- <i>n</i> -decylmethylamine	C ₂₁ H ₄₅ N	[7396-58-9]	6.3
dicocoalkylmethylamines		[61788-62-3]	2
dihydrogenated tallowalkylmethylamines		[61788-63-4]	38
Trialkyl			
tri- <i>n</i> -octylamine	C ₂₄ H ₅₁ N	[1116-76-3]	34.6
tri- <i>n</i> -dodecylamine	C ₃ H ₇₅ N	[102-87-4]	9
tri- <i>n</i> -hexadecylamines		[67701-00-2]	3

Boiling points of fatty amines have been reported (13,27–29). A direct correlation between molecular weight and boiling point is observed. Mixtures of primary fatty amines prepared from fats and oils can be separated into component amines by fractional distillation; an approximately 10 °C increment in boiling point per carbon in the chain length is maintained throughout the series. Symmetrical secondary and tertiary fatty amines have a tendency to decompose during distillation and boiling point data are not reliable. The presence of residual catalyst from the preparation of these amines can lead to decomposition products during distillation.

Fatty amines are insoluble in water, but soluble in organic solvents to varying degrees (26–29). Water, however, is soluble in the amines, and hydrates are formed. Solubility in organic solvents is dependent on solvent polarity and temperature. The solubilities of primary amine acetates and

hydrochlorides have been documented (29). Fatty amine acetates, available commercially, are very soluble in 95° ethanol.

The unshared pair of electrons on the nitrogen atom provides the basic character to the fatty amines. Basicity of amines has been determined as (29):

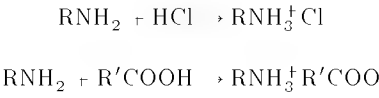


Water and carbon dioxide from the atmosphere can be absorbed by the amines to form hydrates and carbamates, from primary and secondary amines, respectively.

Chemical Reactions

General amine chemistry is applicable to fatty amines. Many chemical reactions using fatty amines as reactive intermediates are run on an industrial scale to produce a wide range of important products. Important industrial reactions are as follows.

Salt Formation. Amines react with inorganic and organic acids.

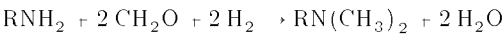


Methylation of Primary and Secondary Fatty Amines. This is done by the Leuckart reaction (1,30) or reductive methylation (1,29,31,32).

Leuckart reaction

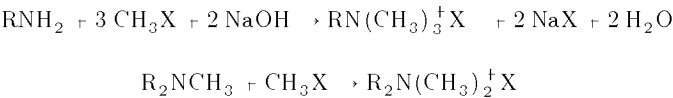


Reductive methylation



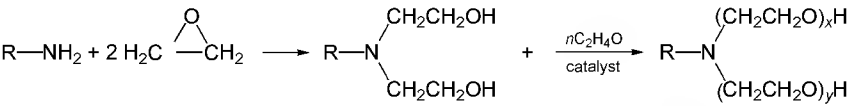
The Leuckart reaction uses formic acid as reducing agent. Reductive alkylation using formaldehyde, hydrogen, and catalyst, usually nickel, is used commercially to prepare methylated amines. These tertiary amines are used to prepare quaternary ammonium salts.

Quaternization. Quaternary ammonium compounds are formed by alkylation of alkyl, alkyldimethyl, dialkyl, and dialkylmethyl fatty amines with methyl chloride, dimethyl sulfate, or benzyl chloride (1,3,7,12,29).



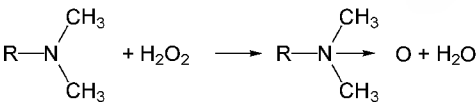
A wide variety of quaternaries can be prepared. Alkylation with benzyl chloride may produce quaternaries that are biologically active, namely, bactericides, germicides, or algacides. Reaction of a tertiary amine with chloroacetic acid produces an amphoteric compound, a betaine.

Ethoxylation and Propoxylation. Ethylene oxide [75-21-8] or propylene oxide [75-56-9] add readily to primary fatty amines to form bis(2-hydroxyethyl) or bis(2-hydroxypropyl) tertiary amines; secondary amines also react with ethylene or propylene oxide to form 2-hydroxyalkyl tertiary amines (1,3,7,33–36). The initial addition is completed at approximately 170°C. Additional ethylene or propylene oxide can be added by using a basic catalyst, usually sodium or potassium hydroxide.



Ethylene oxide adds to the bis(2-hydroxyethyl) tertiary amine in a random fashion where $x + y = n + 2$. Ethoxylated amines, varying from strongly cationic to very weakly cationic in character, are available containing up to 50 mol of ethylene oxide/mol of amine. Ethoxylated fatty amine quaternaries, cationic surfactants (both chloride from methyl chloride and acetate from acetic acid), are also available.

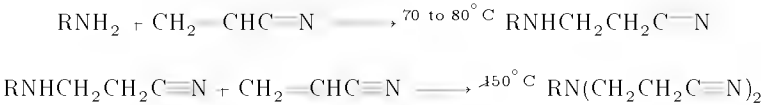
Oxidation by Hydrogen Peroxide. This reaction produces amine oxides (qv) (1,7,33,34,36).



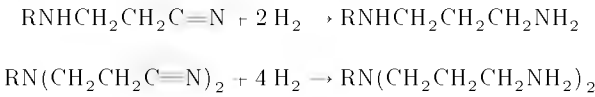
Fatty amine oxides are most frequently prepared from alkyldimethylamines by reaction with hydrogen peroxide. Aqueous 2-propanol is used as solvent to prepare amine oxides at concentrations of 50–60°. With water only as a solvent, amine oxides can only be prepared at lower concentrations because aqueous solutions are very viscous. Fatty amine oxides are weak cationic surfactants.

Cyanoethylation. The reaction of primary fatty amines with acrylonitrile followed by hydrogenation produces diamines and triamines (4,7,31,32,37,38).

Cyanoethylation (Michael addition)



Hydrogenation



The addition of 1 mol of acrylonitrile (Michael addition) to the primary amine is an exothermic reaction, carried out at moderate temperature (70°C), either neat or using a polar solvent (water or low molecular weight alcohol). A fatty diamine, containing one primary and one secondary nitrogen, is formed when the nitrile adduct is catalytically hydrogenated. It is possible to add a second mole of acrylonitrile to the initial mononitrile adduct. However, the second addition does not occur as readily. Reduction of a dinitrile adduct forms a triamine, which contains one tertiary and two primary amino groups. Reduction of the nitrile can be problematic in that varying degrees of decyanoethylation occur depending on catalyst and temperature used during reduction.

Primary fatty amines also add (Michael addition) to esters of acrylic acid, $\text{H}_2\text{C}=\text{CHCOOH}$, methacrylic acid, $\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{COOH}$, or crotonic acid, $\text{CH}_3\text{CH}=\text{CHCOOH}$. Hydrolysis of the Michael ester forms an amphoteric surfactant. Crotonic acid can be used to form the amphoteric compound

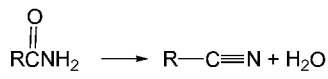
directly.

Manufacture

The principal industrial production route used to prepare fatty amines is the hydrogenation of nitriles, a route which has been used since the 1940s. Commercial preparation of fatty amines from fatty alcohols is a fairly new process, created around 1970, which utilizes petrochemical technology, Ziegler or Oxo processes, and feedstock.

In addition to the nitrile and alcohol routes for fatty amine preparation, processes have been described by Unocal and Pennwalt Corporation, using an olefin and secondary amine (14–16); by Texaco Inc., hydrogenation of nitroparaffins (17–20); by Onyx Corporation, reaction of an alkyl halide with secondary amines (21,22); by Henkel & Cie, GmbH, reduction of an ester in the presence of a secondary amine (23); by catalytic hydroammonolysis of carboxylic acids (24); and by the Hofmann rearrangement (25).

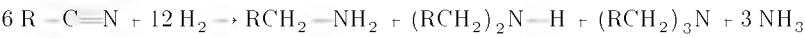
Nitrile Process. Fatty nitriles are readily prepared via batch, liquid-phase, or continuous gas-phase processes from fatty acids and ammonia. Nitrile formation is carried out at an elevated temperature (usually >250°C) with catalyst. An ammonia soap which initially forms, readily dehydrates at temperatures above 150°C to form an amide. In the presence of catalyst, zinc (ZnO) for batch and bauxite for continuous processes, and temperatures >250°C, dehydration of the amide occurs to produce nitrile. Removal of water drives the reaction to completion.



Hydrogenation of fatty nitrile to amine can be either a batch or continuous process (39–42). For preparing primary amines, ammonia is used to suppress secondary amine formation, at a minimum partial pressure of ~1 MPa (150 psig). Batch hydrogenation of a nitrile produces primary amine at 96% purity with low secondary (1.5%) and tertiary (<1%) amine levels (39). Reduction of the nitrile is carried out at elevated temperature (from 50 to 200°C), using hydrogen gas at high pressure, 3.5 MPa (500 psig) and higher total pressure of ammonia and hydrogen gases, in the presence of various catalysts. Catalysts useful for nitrile reduction include (1) aluminum–nickel Raney alloy (39), (2) Raney cobalt (40,43,44), (3) zinc–chromium or zinc–aluminum (41), (4) Raney nickel (42,45), (5) cobalt, copper, and chromium pellets (46), and (6) various nickel-supported catalysts (47–49).

A mixture of primary and secondary amines is formed when ammonia is not used during the nitrile reduction. It is possible to prepare high purity secondary amines by carrying the reduction out at low pressure and passing hydrogen through the reaction in a batch process (47,48), $2 \text{RNH}_2 \rightarrow \text{R}_2\text{NH} + \text{NH}_3$. A nickel–diatomaceous earth catalyst has been used at 220°C at low pressure and hydrogen purge to prepare secondary amines in high yield. Ammonia is removed continuously to drive the reaction to completion. The selectivity to secondary amine can be further enhanced by adding small amounts of an aliphatic carboxylic acid amide (48). Cobalt or copper chromite catalysts are also used to prepare secondary amines (1). Imines ($\text{RCH}=\text{NH}$ and $\text{RCH}=\text{NCH}_2\text{R}$) are suggested as intermediates in the process (3).

Symmetrical tertiary amines can be prepared in an analogous manner to secondary amines (1). Catalytic hydrogenation at elevated temperature and low pressure with a hydrogen purge produces a mixture of primary, secondary, and tertiary amines.



The rate of reaction slows down as the conversion to tertiary amine increases and primary amine concentrations drop below 1%. Conversion to 100% tertiary amine is difficult.

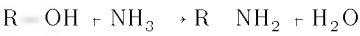
Alkyldimethyl and dialkylmethyl tertiary amines are commercially available. These amines are prepared by reductive methylation of primary and secondary amines using formaldehyde and nickel catalysts (1,3,47,48). The asymmetrical tertiary amines are used as reactive intermediates for preparing many commercial products.

Catalytic hydrogenation of raw materials prepared from natural fats and oils can be difficult because impurities are present which can affect the catalyst performance. Tallow fatty acid can contain the following catalyst poisons in differing amounts: sulfur, phosphorus, chlorine, and nitrogen (49). These catalyst poisons are removed to varying degrees during the refining process. Thus, catalyst loading levels can change from batch to batch.

Homogeneous and heterogenous catalysts which selectively or partially hydrogenate fatty amines have been developed (50). Selective hydrogenation of cis and trans isomers, and partial hydrogenation of polyunsaturated moieties, such as linoleic and linolenic to oleic, is possible.

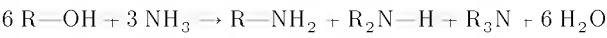
Alcohol Process. Fatty alcohols react with ammonia, or a low molecular weight primary or secondary amine, to form fatty amines. The fatty alcohols can be prepared from natural sources, fats and oils, or may be petroleum derived. Processes for manufacturing the fatty alcohol vary and depend on the raw material source, natural or petrochemical. Natural fatty acids, or preferably methyl esters of fatty acids, are catalytically reduced to alcohols by high pressure >20 MPa (3000 psig) and temperature (250–300°C) hydrogenation using copper chromite catalyst (11,51). Synthetic fatty alcohols are prepared using the Oxo (hydroformylation, reaction of carbon monoxide and hydrogen) or the Ziegler (ethylene and triethylaluminum) processes (10).

Primary amines can be prepared from alcohols and an excess of ammonia (52–55). Either a batch or continuous process can be used. The reaction is run at elevated temperature (50–340°C) and high pressure, 3.5 MPa (500 psig), with an ammonia-to-alcohol ratio of 5:1 to 30:1.



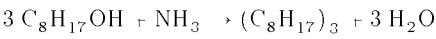
For example, a secondary alcohol of an average molecular weight of 202, containing 12–14 carbon atoms, is introduced into a reaction tube packed with a cobalt promoted zirconium catalyst on alumina at a rate of 60 mL/h along with liquid ammonia (90 mL/h) and hydrogen (5 L/h) to produce an amine mixture composed of 92.2% primary amine, 2.15% secondary and tertiary amines, and 5.7% unreacted alcohol (52). The reaction, at 180–190°C and 24 MPa (~3500 psig), is run by withdrawing the liquid reaction product from the bottom of the reactor.

Secondary amines can be prepared from an alcohol and either ammonia (56) or primary amine (57).



When a mixture of long-chain alcohols, Neodol 25 (Shell Chemical Company) and Alfol 1618 [Conoco Inc. (E. I. du Pont de Nemours & Co.)], containing a nickel catalyst (Girdler G49B) is heated at 190°C for six hours with a hydrogen and ammonia sparge, a mixture of amines is formed: 3.7% primary, 76.7% secondary, and 16.9% tertiary (56). This is similar to what is observed when fatty nitriles are reduced at low pressure and high temperature. High purity secondary amines have been prepared by reaction of an alcohol with a primary amine at elevated temperature (to 250°C) and low pressure (atmospheric) using a selective catalyst; use of copper, nickel, and a noble metal catalyst such as platinum, palladium, or ruthenium is recommended (57). For example, dilaurylamine was prepared at 92% purity by reaction of lauryl alcohol with laurylamine in the presence of a ruthenium catalyst.

Batch or continuous processes can be used to prepare tertiary amines from alcohols and ammonia or a secondary amine, such as, dimethylamine.



Trioctylamine has been prepared, in a continuous process, using 5,200 kg of *n*-octanol, 100 kg of copper formate catalyst, 500 kg of *n*-octylamine, 10 kg of calcium hydroxide, and 240 kg of ammonia (58). Ammonia was added over a 10-h period while 10 m³ of hydrogen/h was passed through the reactor at a reaction temperature of 180–200°C. The final product was composed of 94% trioctylamine, 2% dioctylamine, 1% octylamine, and 0.5% *n*-octanol. A

tertiary amine was prepared from dodecanol and dimethylamine using a nickel promoted-catalyst.



Thus, a 94% conversion to dimethyldodecylamine was obtained in five hours using nickel catalyst promoted with chromium and iron at 180°C and 1.1 MPa (160 psig) (59). Catalysts used for preparing amines from alcohols include: cobalt promoted with zirconium, lanthanum, cerium, or uranium (52); the metals and oxides of nickel, cobalt, and or copper (53,54,56,60,61); metal oxides of antimony, tin, and manganese on alumina support (55); copper, nickel, and a metal belonging to the platinum group 8–10 (57); copper formate (58); nickel promoted with chromium and or iron on alumina support (53,59); and cobalt, copper, and either iron, zinc, or zirconium (62).

Commercial Availability

United States consumption of fatty nitrogen derivatives amounted to 231,100 t in 1985 (63) and 200,000 t in 1984 (8). With an average annual growth rate anticipated at 3.7%, U.S. consumption was estimated to be 280,000 t in 1990. Fatty amine usage was 15,500 t (6.7% of the nitrogen derivative market) in 1985 and expected to increase to 20,500 t through 1990 (5.6% yr). Fatty amines were used as intermediates (1985 data with percentage of total market) for the preparation of quaternaries [86,700 t (37.5%)], fatty diamine polyamine condensates [20,000 t (8.6%)], amine oxides [13,500 t (5.8%)], betaines [4,300 t (1.9%)], and ethoxylated amines [2,500 t (1%)]. Fatty amine end use pattern for 1985 was as follows: ore flotation, 55%; biocide corrosion inhibitor, 24%; metal working, 5%; and others, 16% of the market (64). It was estimated in 1986 that plant capacities of the major U.S. producers of fatty amines and derivatives were 207,000 t (64). Thus, plant expansion was needed to keep up with the increasing usage of fatty amines and nitrogen derivatives. Plant expansions have occurred at Akzo Chemicals Inc. (65), Ethyl Corporation (66,67), Humko Chemical (Witco Corporation) (68), Jetco Chemicals, Inc. (The Procter & Gamble Company) (69), Tomah Products, Inc. (Exxon Chemical Company) (70), and Sherex Chemical Co. (71,72). The major source of raw materials for the preparation of fatty amines is fats and oils such as tallow, and coconut, soya, and palm oils. Ethyl Corporation uses petrochemicals as raw materials to prepare alkyl dimethyl and dialkylmethyl tertiary fatty amines, trademarked as ADMA and DAMA products, which can be supplied as single-carbon chain-length cuts or custom blends (13). Commercially available high purity fatty amines are listed in Table 3. Cost of the amines can vary owing to supply of raw materials.

Table 3. Commercially Available Fatty Amines

Fatty amine (common name)	Molecular formula	CAS Registry Number	Trade name	Manufacturer	Appearance
Primary amines					
2-ethylhexylamine	C ₈ H ₁₉ N	[104-75-6]	Armeen L8D	Akzo	liquid
cocoalkylamines		[61788-46-3]	Armeen CD	Akzo	liquid
			Alamine 21D	Henkel	
			Kemamine P-650	Humko	liquid
			Jet Amine PCD	Jetco	liquid
			Adogen 160-D	Sherex	liquid
dodecylamine	C ₁₂ H ₂₇ N	[124-22-1]	Armeen 12D	Akzo	semisolid
			Alamine 4D	Henkel	
			Adogen 163-D	Sherex	liquid
hexadecylamine	C ₁₆ H ₃₅ N	[143-27-1]	Armeen 16D	Akzo	solid
			Kemamine P-880D	Humko	solid
octadecylamine	C ₁₈ H ₃₉ N	[124-30-1]	Armeen 18D	Akzo	solid
			Alamine 7D	Henkel	
			Kemamine P-990D	Humko	solid
			Adogen 142-D	Sherex	solid
oleylamine	C ₁₈ H ₃₇ N	[112-90-3]	Armeen OD	Akzo	semisolid
			Alamine 11D	Henkel	
			Kemamine P-989D	Humko	liquid
			Jet Amine POD	Jetco	liquid
			Adogen 172-D	Sherex	liquid
soyaalkylamines		[61970-18-9]	Armeen SD	Akzo	paste
			Jet Amine PSD	Jetco	paste
			Adogen 115-D	Sherex	liquid
tallowalkylamines		[61790-33-8]	Armeen TD	Akzo	solid
			Alamine 26D	Henkel	
			Kemamine P-974D	Humko	paste
			Jet Amine PTD	Jetco	solid
			Adogen 170-D	Sherex	paste
			Tomah P-2B	Tomah	
hydrogenated tallowalkylamines		[61788-45-2]	Armeen HTD	Akzo	solid
			Alamine H26D	Henkel	
			Kemamine P-970D	Humko	solid
			Jet Amine PHTD	Jetco	solid
			Adogen 140-D	Sherex	solid
eicosylamine docosylamine	(C ₂₀ –C ₂₂)	[60800-66-0]	Kemamine P-190D and P-150D	Humko	solid
			Adogen 101	Sherex	solid
Secondary amines					
didecylamine	C ₂₀ H ₄₃ N	[1120-49-6]	Armeen 2-10	Akzo	liquid
dicocoalkylamines		[61789-76-2]	Armeen 2C	Akzo	solid
			Jet Amine 2C	Jetco	solid
diisotridecylamine	C ₂₂ H ₅₅ N	[57157-80-9]	Adogen 283	Sherex	liquid
dioctadecylamine	C ₃₀ H ₇₅ N	[112-99-2]	Armeen 2-18	Akzo	solid
ditallowalkylamines		[68783-24-4]	Armeen 2T	Akzo	solid
dihydrogenated tallowalkylamines		[61789-79-5]	Armeen 2HT	Akzo	solid
			Kemamine S-970	Humko	solid
			Jet Amine 2HT	Jetco	solid
			Adogen 240	Sherex	solid
dieicosylamine didocosylamines		[53529-35-4]	Kemamine S-190	Humko	solid

Tertiary amines					
Alkyldimethylamines					
dimethyloctylamine	C ₁₀ H ₂₃ N	[7378-99-6]	ADMA-8	Ethyl	liquid
decyldimethylamine	C ₁₂ H ₂₇ N	[1120-24-7]	ADMA-10	Ethyl	liquid
dimethyldodecylamine	C ₁₄ H ₃₁ N	[112-18-5]	Armeen DM12D	Akzo	liquid
cocoalkyldimethylamines		[61788-93-0]	ADMA-12	Ethyl	liquid
			Armeen DMCD	Akzo	liquid
			Kemamine T-6502D	Humko	liquid
			Jet Amine DMCD	Jetco	liquid
dimethyltetradecylamine	C ₁ H ₃₅ N	[112-75-4]	ADMA-14	Ethyl	liquid
dimethylhexadecylamine	C ₁₈ H ₃₉ N	[112-69-6]	Armeen DM16D	Akzo	liquid
dimethyloctadecylamine	C ₂₀ H ₄₃ N	[124-28-7]	ADMA-16	Ethyl	liquid
			Armeen DM18D	Akzo	liquid
			ADMA-18	Ethyl	liquid
			Kemamine T-9902D	Humko	liquid
dimethyloleylamine	C ₂₀ H ₄₁ N	[28061-69-0]	Armeen DMOD	Akzo	liquid
dimethylsoyaalkylamines		[61788-91-8]	Jet Amine DMOD	Jetco	liquid
			Armeen DMSD	Akzo	liquid
			Kemamine T-9972D	Humko	liquid
dimethyltallowalkylamines		[68814-69-7]	Jet Amine DMSD	Jetco	liquid
			Armeen DMTD	Akzo	liquid
			Kemamine T-9742D	Humko	liquid
			Jet Amine DMTD	Jetco	liquid
dimethylhydrogenated tallowalkylamines		[61788-95-2]	Armeen DMHTD	Akzo	liquid
dimethyleicosylamine		[93164-85-3]	Kemamine T-9702D	Humko	liquid
			Jet Amine DMHTD	Jetco	liquid
			Kemamine T-1902D	Humko	solid
dimethyldocosylamines					
Dialkylmethylamines					
di(C ₈ –C ₁₀)methylamine	C ₁₇ H ₃₇ N	[4455-26-9]	DAMA-810	Ethyl	liquid
didecylmethylamine	C ₁₉ H ₄₁ N	[22020-14-0]			
	C ₂₁ H ₄₅ N	[7396-58-9]			
	C ₂₁ H ₄₅ N	[7396-58-9]	Armeen M2-10D	Akzo	liquid
	dicocoalkylmethylamines		[61788-62-3]	DAMA-1010	Ethyl
Armeen M2C				Akzo	liquid
Kemamine T-6501				Humko	liquid
Jet Amine M2C				Jetco	solid
Adogen 369				Sherex	liquid
dioctadecylmethylamine	C ₃₇ H ₇₇ N	[4088-22-6]	Adogen 349	Sherex	solid
dihydrogenated tallowalkylmethylamines		[61788-63-4]	Armeen M2HT	Akzo	solid
			Kemamine T-9701	Humko	solid
			Jet Amine M2HT	Jetco	solid
			Adogen 343	Sherex	solid
			Trialkylamines		
trioctylamine	C ₂₄ H ₅₁ N	[1116-76-3]	Alamine 336	Henkel	liquid
tri(isooctyl)amine	C ₂₄ H ₅₁ N	[25549-16-0]	Adogen 381	Sherex	liquid
tri(C ₈ –C ₁₀)amines		[68814-95-9]	Adogen 364	Sherex	liquid
tri(isodecyl)amine	C ₃₀ H ₃ N	[35723-89-8]	Adogen 382	Sherex	liquid
trilaurylamine	C ₃ H ₇₅ N	[102-87-4]	Armeen 3-12	Akzo	liquid
tri(isotridecyl)amine	C ₃₉ H ₈₁ N	[35723-83-2]	Alamine 304	Henkel	liquid
			Adogen 383	Sherex	liquid
			Armeen 3-16	Akzo	solid
trioctadecylamine	C ₅₄ H ₁₁₁ N	[102-88-5]	Adogen 340	Sherex	solid
Diamines					
N-cocoalkyltrimethylenediamines		[61791-63-7]	Duomeen CD	Akzo	semisolid
			Diam 21D	Henkel	
			Kemamine D-650	Humko	liquid
			Jet Amine DC	Jetco	liquid
N-tallowalkyltrimethylenediamines		[61791-55-7]	Adogen 560	Sherex	liquid
			Duomeen T	Akzo	solid
			Diam 26	Henkel	
			Kemamine D-974	Humko	solid
			Jet Amine DT	Jetco	paste
			Adogen 570-S	Sherex	solid
			Tallow Diamine	Tomah	
N-hydrogenated tallowalkyltrimethylenediamines		[37231-11-1]	Kemamine D-970	Humko	solid
N-oleyl-1,3-diaminopropane	C ₂₁ H ₄₄ N ₂	[7173-62-8]	Adogen 540	Sherex	flakes
			Duomeen O	Akzo	liquid
			Diam 11	Henkel	
			Kemamine D-989	Humko	liquid
			Jet Amine DO	Jetco	liquid
N-eicosyl-1,3-diaminopropane	N-docosyl-1,3-diaminopropanes	[89234-29-7]	Adogen 572	Sherex	liquid
			Kemamine D-150	Humko	solid
N,N,N'-trimethyl-N'-tallowalkyltrimethy		[68783-25-5]	Duomeen TTM	Akzo	liquid

lenediamines				
		<i>Triamines</i>		
N-tallowalkyl dipropylene tri amines	[61791-57-9]	Triameen T	Akzo	paste
		Tallow triamine	Tomah	
		<i>Tetramines</i>		
N-tallowalkyl tripropylene tetra mine		Tallow tetramine	Tomah	

Fatty amine products are normally shipped in 55-gal (208 L), lined and unlined, steel drums or in tank cars or tank trucks for bulk shipments. High melting amines can be flaked and shipped in cardboard cartons or paper bags. The amines are corrosive to skin and eyes. Protective splash goggles and gloves should be worn when handling these materials.

Specifications of commercially available fatty amines are listed in product bulletins which are available from the manufacturers (31,73–80). For primary amines, specifications can include minimum and maximum values for the following: the percentage of primary and apparent secondary amines, color (Gardner), equivalent weight, amine number, moisture, and iodine value (IV). Secondary amine specifications, in addition to the above, have a minimum value for apparent secondary amine content, while tertiary amines would have specifications on a minimum percentage of tertiary and maximum percentage of primary and secondary amine content. Specifications for diamines can include a minimum percentage of diamine content. Some product bulletins in addition to listing specifications give typical analytical values.

Analysis

To analyze fatty amines, both wet and instrumental methods of analysis are used. Wet methods routinely used are: total amine value (ASTM Method D2073); combining weight or neutralization equivalent; primary, secondary, and tertiary amine content (ASTM Method D2083); moisture, Karl-Fischer (ASTM Method D2072); and iodine value, measure of unsaturation (ASTM Method D2075). These provide important information on physical and chemical characteristics of the amine products used in various application areas (8,76,81). In addition to the ASTM methods available, the American Oil Chemists' Society has developed methods of analysis for fatty amines (82).

Instrumental methods of analysis provide information about the specific composition and purity of the amines. Qualitative information about the identity of the product (functional groups present) and quantitative analysis (amount of various components such as nitrile, amide, acid, and determination of unsaturation) can be obtained by infrared analysis. Gas chromatography (gc), with a liquid phase of either Apiezon grease or Carbowax, and high performance liquid chromatography (hplc), using silica columns and solvent systems such as isooctane, methyl *tert*-butyl ether, tetrahydrofuran, and methanol, are used for quantitative analysis of fatty amine mixtures. Nuclear magnetic resonance spectroscopy (nmr), both proton (¹H) and carbon-13 (¹³C), which can be used for qualitative and quantitative analysis, is an important method used to analyze fatty amines (8,81).

Health and Safety Factors

Skin and Eye Irritation. Fatty alkylamines are generally considered to be irritating to both the skin and eyes (83). The severity or degree of irritation is usually dependent on the type of alkylamine, concentration of the chemical, time of exposure to the chemical, and sensitivity to the chemical. A small percentage of the population who come into contact with fatty amines may develop a skin hypersensitivity to certain amines and diamines.

Alkylamines and diamines are generally classified as corrosive to the skin based on results from laboratory animal (rabbit) studies performed in accordance with the Department of Transportation (DOT) test method (84); rabbits are considered to be especially sensitive to alkylamines which even at low concentrations can induce skin redness and swelling. Oleylamine has been shown to induce mild to moderate skin irritation in laboratory rats when applied at a concentration of 0.3% in mineral oil (Chemical Manufacturer's Association, 1985). Fatty amines which contain alkyl chains of 10–14 carbons are considered more irritating than related products which contain alkyl chains of 14–18 carbon atoms. Ethoxylation generally decreases the irritation potential of alkylamines.

Oral Toxicity. Depending on the chemical class, most fatty amines range from moderately toxic to practically nontoxic by acute oral ingestion. Laboratory animal testing has revealed that the amines and diamines can induce irritation and damage to the gastrointestinal tract. The acute oral LD₅₀ of cocoalkyldiamine in rats is less than 200 mg/kg body weight (Armac Test Data, 1981), whereas the corresponding value for dihydrogenated tallowalkylmethylamine (Akzo Chemie Data, 1984) is greater than 5,000 mg/kg. Products which have LD₅₀ values greater than 5000 mg/kg are considered practically nontoxic by accidental ingestion.

Dermal Toxicity. Fatty alkylamines are not considered especially toxic with regard to skin penetration and systemic absorption into the body; certain polyamines may be absorbed through the skin to a much greater degree. The acute dermal LD₅₀ of decylamine in rabbits has been reported to be 350 mg/kg [RTECS, 1982 (85)]; dialkyl(C₁₄–C₁₈)methylamine has been shown to have an acute dermal LD₅₀ value of greater than 2000 mg/kg in rabbits (Dynamac Corporation, 1988). Products with acute dermal LD₅₀ values greater than 2000 mg/kg are considered to exhibit a low degree of hazard by acute dermal exposure.

Inhalation. Long-chain amines are not considered an inhalation hazard at ambient conditions because of their relatively low volatility. Inhalation of aerosols or heated vapors may result in irritation of the nose, throat, and upper respiratory system. Lower molecular weight and branched-chain amines are more volatile and can cause irritation if inhaled. Volatile amines are easily recognized by their unpleasant, fishy odor.

Uses

Fatty amines and chemical products derived from the amines are used in many industries. Uses for the nitrogen derivatives may be broken down as follows as a percentage of total market: fabric softeners (46%), oil field chemicals (15%), asphalt emulsifiers (10%), petroleum additives (10%), mining (4%), and others (15%) (8).

Amine salts, especially acetate salts prepared by neutralization of a fatty amine with acetic acid, are useful as flotation agents (collectors), corrosion inhibitors, and lubricants (3,8). Amine acetates are commercially available from a number of suppliers: Akzo Chemicals Inc. (Armac) (73); Henkel Corporation (formerly General Mills) (Alamac) (74); Jetco Chemicals Inc. (The Procter & Gamble Company) (Jet Amine) (75); Sherex (Adogen) (76); and Tomah Products (Exxon Chemical Company) (Tomah) (77).

The single largest market use for quaternary fatty amines is in fabric softeners. Monoalkyl quaternaries (chloride) have been used in liquid detergent softener antistat formulations (LDSA), dialkyldimethyl quaternaries (chloride) in the rinse cycle, and dialkyldimethyl quaternaries (sulfate) as dryer softeners.

Another significant use for dialkyldimethyl quaternary ammonium salts and alkylbenzyldimethylammonium salts is in preparing organoclays for use as drilling muds, paint thickeners, and lubricants.

Betaines, or specialty quaternaries, are used in the personal care industry in shampoos, conditioners, foaming, and wetting agents.

Companies producing fatty amine quaternaries include: Akzo Chemicals Inc. (Arquad) (73); Henkel Corporation (formerly General Mills) (Aliquat) (74); Humko Chemical (Witco Corporation) (Kemamine Q) (31); Jetco Chemicals (The Procter & Gamble Company) (Jet Quat) (75); Jordan Chemical Company (PPG Industries) (Jordaquat and specialty quaternaries) (78); Lonza (Barquat and specialty quaternaries) (79); Sherex (Adogen) (76); and Tomah Products (Exxon Chemical Company) (Tomah Q) (77).

A significant use of ethoxylated and propoxylated amines is as antistatic agents (qv) in the textile and plastics industry (86). Ethoxylates are also used in the agricultural area as adjuvants. Ethoxylated fatty amines and derivatives are available from: Akzo Chemicals Inc. (Ethomeen) (73); Henkel Corporation (Trymeen) (87); GAF Chemicals Corporation (Rhône Poulenc) (Katapol) (88); Jetco Chemicals Inc. (The Procter & Gamble Company) (Jet Amine) (75); Mazer Chemicals (PPG Industries) (Mazeen) (89); Sherex (Adogen) (76); and Tomah Products (Exxon Chemical Company) (Tomah E) (77).

Examples of uses for amine oxides include: detergent and personal care areas as a foam booster and stabilizer, as a dispersant for glass fibers, and as a foaming component in gas recovery systems. Commercial suppliers of fatty amine oxides include: Akzo Chemicals Inc. (Aromox) (73), Jordan Chemical Company (PPG Industries) (Jordamox) (78), and Lonza (Barlox) (79).

Important uses for the diamines include: corrosion inhibitors, gasoline and fuel oil additives, flotation agents, pigment wetting agents, epoxy curing agents, herbicides, and asphalt emulsifiers (3,75,77). Fatty diamines, *n*-alkyl-1,3-diaminopropanes, and triamines, *n*-alkyldipropylenetriamines, are available commercially from: Akzo Chemicals Inc. (Duomeen and Triameen) (73), Henkel Corporation (formerly General Mills) (Diam) (74), Humko Chemical (Witco Corporation) (Kemamine) (31), Jetco Chemicals (The Procter & Gamble Company) (Jet Amine) (75), Sherex (Adogen) (76), and Tomah Products (Exxon Chemical Company) (Diamines, Triamines, and Tetramines) (77).

Fatty amines and derivatives are widely used in the oil field, as corrosion inhibitors, surfactants, emulsifying deemulsifying and gelling agents (90). In the mining industry, amines and diamines are used in the recovery and purification of minerals, flotation, and beneficiation. A significant use of fatty diamines is as asphalt emulsifiers for preparing asphalt emulsions. Diamines have also been used as epoxy curing agents, corrosion inhibitors, gasoline and fuel oil additives, and pigment wetting agents. Oleylamine is a petroleum additive useful as a detergent in gasoline (8). In addition, derivatives of the amines, amphoterics, and long-chain alkylamines are used as anionic and cationic surfactants in the personal care industry (91).

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AMINES, AROMATIC

Aniline and its derivatives,
Diaminotoluenes,
Diarylamines,
Methylenedianiline,
Phenylenediamines,

ANILINE AND ITS DERIVATIVES

Aniline (benzenamine) [62-53-3] is the simplest of the primary aromatic amines. It was first produced in 1826 by dry distillation of indigo. In 1840 the same oily liquid was obtained by heating indigo with potash, and it was given the name aniline. The structure of aniline was established in 1843 with the demonstration that it could be obtained by reduction of nitrobenzene.

Aromatic amines can be produced by reduction of the corresponding nitro compound, the ammonolysis of an aromatic halide or phenol, and by direct amination of the aromatic ring. At present, the catalytic reduction of nitrobenzene is the predominant process for manufacture of aniline. To a smaller extent aniline is also produced by ammonolysis of phenol.

Important analogs of aniline include the toluidines, xylydines, anisidines, phenetidines, and its chloro-, nitro-, *N*-acetyl, *N*-alkyl, *N*-aryl, *N*-acyl, and sulfonic acid derivatives.

Physical Properties

Pure, freshly distilled aniline is a colorless, oily liquid that darkens on exposure to light and air. It has a characteristic sweet, aminelike aromatic odor. Aniline is miscible with acetone, ethanol, diethyl ether, and benzene, and is soluble in most organic solvents. Its solubility characteristics in water are as follows:

Temperature, °C	Parts aniline per 100 parts water	Parts water per 100 parts aniline
25	3.5	5.0
90	6.4	9.9

The physical properties of aniline are given in Table 1 and vapor pressure data in Table 2.

Table 1. Physical Properties of Aniline

Property	Value
molecular formula	C ₆ H ₅ N
molecular weight	93.129
boiling point, °C	
101.3 kPa ^a	184.4
4.4 kPa ^a	92
1.2 kPa ^a	71
freezing point, °C	6.03
density, liquid, g/mL	
20–4°C	1.02173
20–20°C	1.022
density, vapor (at bp, air = 1)	3.30
refractive index, <i>n</i> _D ²⁰	1.5863
viscosity, mPa·s (cP)	
20°C	4.35
60°C	1.62
enthalpy of dissociation, kJ/mol ^b	21.7
heat of combustion, kJ/mol ^b	3394
ionization potential, eV	7.70
dielectric constant, at 25°C	6.89
dipole moment at 25°C (calcd), C·m ^c	5.20 × 10 ^{−30}
specific heat at 25°C, J/(g·K) ^b	2.06
heat of vaporization, J/g ^b	478.5
flash point, °C	
closed cup	70
open cup	75.5
ignition temperature, °C	615
lower flammable limit, vol %	1.3

^a To convert kPa to mm Hg, multiply by 7.5.

^b To convert J to cal, divide by 4.184.

^c To convert C·m to debye, multiply by 3 × 10²⁹.

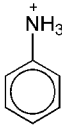
Table 2. Vapor Pressure of Aniline

Temperature, °C	Vapor pressure, kPa ^a	Temperature, °C	Vapor pressure, kPa ^a
175	80	139	28
162	53	119	13
151	40	102	7

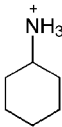
^a To convert kPa to mm Hg, multiply by 7.50.

Chemical Properties

Aromatic amines are usually weaker bases than aliphatic amines as illustrated by the difference in pK_a of the conjugate acids of aniline (1), $pK_a = 4.63$ and cyclohexylamine (2), $pK_a = 10.66$.



(1)



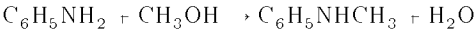
(2)

This is due to a resonance effect. Aniline is stabilized by sharing its nitrogen lone-pair electrons with the aromatic ring. In the anilinium ion, the resonance stabilization is disrupted by the proton bound to the lone pair.

Aromatic amines form addition compounds and complexes with many inorganic substances, such as zinc chloride, copper chloride, uranium tetrachloride, or boron trifluoride. Various metals react with the amino group to form metal anilides; and hydrochloric, sulfuric, or phosphoric acid salts of aniline are important intermediates in the dye industry.

N-Alkylation. A number of methods are available for preparation of *N*-alkyl and *N,N*-dialkyl derivatives of aromatic amines. Passing a mixture of aniline and methanol over a copper–zinc oxide catalyst at 250°C and 101 kPa (1 atm) reportedly gives *N*-methylaniline [100-61-8] in 96% yield (1). Heating aniline with methanol under pressure or with excess methanol produces *N,N*-dimethylaniline [121-69-7] (2,3).

In the presence of sulfuric acid, aniline reacts with methanol to form *N*-methyl- and *N,N*-dimethylaniline. This is a two-step process



and a study of its kinetics (4) shows that reaction rate is proportional to the concentration of aniline in the first step and the concentration of *N*-methylaniline in the second step. With 50% excess methanol, the reaction equilibrium reaches 99% *N,N*-dimethylaniline at 200°C. Reaction is clean with little by-product formation up to 230°C. At higher temperatures, ring alkylation and formation of formaldehyde, from oxidation of methanol, are observed.

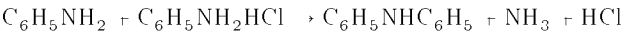
Other catalysts that can be used are boron trifluoride (5), copper–chromium oxides (6), phosphoric acid (7), and silica–alumina (8). Under similar conditions, ethanol yields *N*-ethylaniline [103-69-5] and *N,N*-diethylaniline [91-66-7] (9,10).

N-Alkylation can also be carried out with the appropriate alkyl halide or alkyl sulfate. Reaction of aniline with ethylene, in the presence of metallic sodium supported on an inert carrier such as carbon or alumina, at high temperature and pressure yields *N*-ethyl- or *N,N*-diethylaniline (11). At pressures below 10 MPa (100 atm), the monosubstituted product predominates.

Mixtures of *N*-alkylanilines can usually be separated by fractional distillation. Mixtures of the methyl or ethyl derivatives have also reportedly been separated by converting the *N*-ethyl or the *N*-methyl derivative to the nonvolatile salt with *p*-toluenesulfonic acid (12) or phthalic anhydride (13), followed by distillation.

Catalytic alkylation of aniline with diethyl ether, in the presence of mixed metal oxide catalysts, preferably titanium dioxide in combination with molybdenum oxide and/or ferric oxide, gives 63% *N*-alkylation and 12% ring alkylation (14).

Diphenylamine [122-39-4] is produced by heating aniline with aniline hydrochloride at 290°C and 2 MPa (21 atm) in an autoclave (15).



The by-product ammonia is vented from the reactor during the course of the reaction. Unconverted aniline is distilled off at the end of the reaction and the diphenylamine is washed with aqueous hydrochloric acid to remove trace amounts of aniline. The product is then washed with water and purified in a refining still.

The use of ammonium fluoroborate (NH_4BF_4) as a catalyst for this reaction, is claimed to be advantageous, since the catalyst can be recycled and is noncorrosive to ferrous metals (16).

Diphenylamine can also be produced by passing the vapors of aniline over a catalyst such as alumina, or alumina impregnated with ammonium fluoride (17). The reaction is carried out at 480°C and about 700 kPa (7 atm). Conversion per pass, expressed as parts diphenylamine per 100 parts of reactor effluent, is low (18–22%), and the unconverted aniline must be recycled. Other catalysts disclosed for the vapor-phase process are alumina modified with boron trifluoride (18), and alumina activated with boric acid or boric anhydride (19).

Ring Alkylation. The aromatic ring undergoes alkylation under certain conditions. For example, 2-ethylaniline [103-69-5], 2,6-diethylaniline [579-66-8], or a mixture of the two are obtained in high yield when aniline is heated with ethylene in the presence of aluminum–anilide catalyst (formed by heating aluminum and aniline) at 330°C and 4–5 MPa (40–50 atm) (20). *N*-Ethylaniline is alkylated in a similar manner, but at 205°C yields only *N*-ethyl-2-ethylaniline [578-54-1]. Other olefins can also be used to form ring-alkylated products, but the reaction rate decreases as the molecular weight of the olefin increases. A number of patents, claiming a variety of catalysts, have been issued in this area (21–24).

N-Alkylaniline and *N,N*-dialkylaniline hydrochlorides can be rearranged to *C*-alkyl anilines by heating the salts to 200–300°C. In this reaction, known as the Hofmann-Martius rearrangement, the alkyl group preferentially migrates to the para position. If this position is occupied, the ortho position is alkylated.

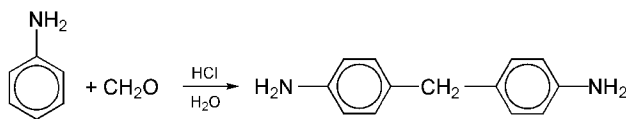
Acylation. Aromatic amines react with acids, acid chlorides, anhydrides, and esters to form amides. In general, acid chlorides give the best yield of the pure product. The reaction with acetic, propionic, butanoic, or benzoic acid can be catalyzed with phosphorus oxychloride or trichloride.

N-Phenylsuccinimide [83-25-0] (succinil) is obtained in essentially quantitative yield by heating equivalent amounts of succinic acid and aniline at 140–150°C (25). The reaction of a primary aromatic amine with phosgene leads to formation of an arylcarbamoyl chloride, that when heated loses hydrogen chloride to form an isocyanate. Commercially important isocyanates are obtained from aromatic primary diamines.

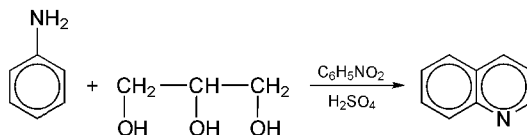
Conversion of aniline to acetanilide [103-84-4], by reaction with acetic anhydride, is a convenient method for protecting the amino group. The acetyl group can later be removed by acid or base hydrolysis.

Condensation. Depending on the reaction conditions, a variety of condensation products are obtained from the reaction of aromatic amines with aldehydes, ketones, acetals, and orthoformates.

Primary aromatic amines react with aldehydes to form Schiff bases. Schiff bases formed from the reaction of lower aliphatic aldehydes, such as formaldehyde and acetaldehyde, with primary aromatic amines are often unstable and polymerize readily. Aniline reacts with formaldehyde in aqueous acid solutions to yield mixtures of a crystalline trimer of the Schiff base, methylenedianilines, and polymers. Reaction of aniline hydrochloride and formaldehyde also yields polymeric products; and under certain conditions, the predominant product is 4,4'-methylenedianiline [101-77-9] (26), an important intermediate for 4,4'-methylenabis(phenylisocyanate) [101-68-8], or MDI (see AMINES, AROMATIC AMINES, METHYLENEDIANILINE).

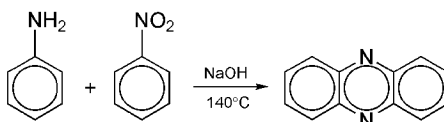


Cyclization. Aniline, nitrobenzene, and glycerol react under acid catalysis (Skraup synthesis) to form quinoline [91-22-5] (27).

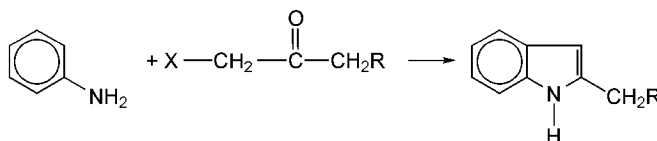


By substituting paraldehyde for glycerol, 2-methylquinoline [27601-00-9] may be synthesized. The Skraup synthesis is regarded as an example of the broader Doebner-von Miller synthesis. In the case of the Skraup synthesis, the glycerol undergoes an acid-catalyzed dehydration to provide a small concentration of acrolein that is the reactive species. If acrolein itself is used as a reactant, it would polymerize. Crotonaldehyde is the reactive intermediate in the Doebner-von Miller synthesis (28).

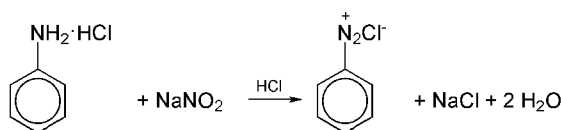
Many substituted quinolines are intermediates for antimalarials. The 2,4-di-substituted quinolines are produced from aniline and 1,3-diketones by the Combes quinoline synthesis (28). The reaction of aniline with nitrobenzene in the presence of dry sodium hydroxide at 140°C leads to formation of phenazine [92-82-0] and by-products (Wohl-Aue synthesis) (29).



Aromatic amines react with 1-haloketones or 1-hydroxyketones to yield substituted indoles. This reaction is known as the Bischler indole synthesis (30).



Reaction with Nitrous Acid. Primary, secondary, and tertiary aromatic amines react with nitrous acid to form a variety of products. Primary aromatic amines form diazonium salts.



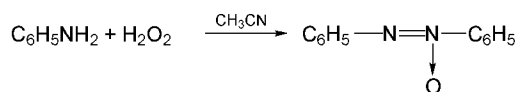
Secondary aromatic amines form *N*-nitrosamines and tertiary aromatic amines undergo ring nitrosation to yield *C*-nitroso products.

Aromatic diazonium salts are usually not isolated and react further to yield the desired product. Their reactions can be grouped in two categories: (1) those in which nitrogen is lost and the diazonium group is replaced by hydroxyl, hydrogen, nitrile, halogen, or aryl groups; and (2) those in which the diazonium ion can act as an electrophile in aromatic substitution reactions, that is, coupling reactions, with an activated aromatic compound.

Coupling of the diazonium salts with phenols and amines forms the basis for manufacture of a number of commercial dyes.

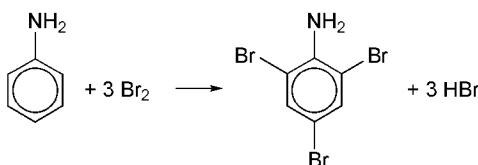
Oxidation. Aromatic amines can undergo a variety of oxidation reactions, depending on the oxidizing agent and the reaction conditions. For example, oxidation of aniline can lead to formation of phenylhydroxylamine, nitrosobenzene, nitrobenzene, azobenzene, azoxybenzene or *p*-benzoquinone. Oxidation was of great importance in the early stages of the development of aniline and the manufacture of synthetic dyes, such as aniline black and Perkin's mauve.

Nitroso compounds are formed selectively via the oxidation of a primary aromatic amine with Caro's acid [7722-86-3] (H₂SO₅) or Oxone (Du Pont trademark) monopersulfate compound (2KHSO₅·KHSO₄·K₂SO₄); aniline black [13007-86-8] is obtained if the oxidation is carried out with salts of persulfuric acid (31). Oxidation of aromatic amines to nitro compounds can be carried out with peroxytrifluoroacetic acid (32). Hydrogen peroxide with acetonitrile converts aniline in a methanol solution to azoxybenzene [495-48-7] (33), perborate in glacial acetic acid yields azobenzene [103-33-3] (34).



Oxidation of aniline with a mixture of manganese dioxide and sulfuric acid has been used commercially for production of *p*-benzoquinone [106-51-4] (35).

Halogenation. The presence of the amino group activates the ortho and para positions of the aromatic ring and, as a result, aniline reacts readily with bromine or chlorine. Under mild conditions, bromination yields 2,4,6-tribromoaniline [147-82-0].



Controlled halogenation can be achieved by halogenation of the *N*-acetyl derivative of the aromatic amine, followed by hydrolysis of the acetyl

group.

Chlorine in the presence of hydrogen chloride in an anhydrous organic solvent yields 2,4,6-trichloroaniline [634-93-5] (36,37). A mixture of aniline vapor and chlorine, diluted with an inert gas, over activated carbon at 400°C yields *o*-chloroaniline [95-51-2] (38). Aniline when treated with chlorine gas, in an aqueous mixture of sulfuric acid and acetic acid, at 105–115°C gives an 85–95° yield of *p*-chloranil [118-75-2] (39).

Sulfonation. Aniline reacts with sulfuric acid at high temperatures to form *p*-aminobenzenesulfonic acid (sulfanilic acid [121-57-3]). The initial product, aniline sulfate, rearranges to the ring-substituted sulfonic acid (40). If the para position is blocked, the *o*-aminobenzenesulfonic acid derivative is isolated. Aminosulfonic acids of high purity have been prepared by sulfonating a mixture of the aromatic amine and sulfolane with sulfuric acid at 180–190°C (41).

In the reaction of anilinium sulfate [542-16-5] with fuming sulfuric acid, the major products are *m*- and *p*-aminobenzenesulfonic acid with less than 2° of the ortho isomer. With excess concentrated sulfuric acid (96.8–99.9°) at 60–100°C, the sulfate salt gives mainly the ortho and para isomers of the sulfonic acid (42).

When *p*-aminobenzenesulfonic acid is heated with sulfuric acid and phosphorus pentoxide, 2-amino-1,3,5-benzenetrisulfonic acid [64775-08-4] is the product (43).

Nitration. Direct nitration of aromatic amines with nitric acid is not a satisfactory method, because the amino group is susceptible to oxidation. The amino group can be protected by acetylation, and the acetylamino derivative is then used in the nitration step. Nitration of acetanilide in sulfuric acid yields the 4-nitro compound that is hydrolyzed to *p*-nitroaniline [100-01-6].

Nitration of aromatic amines with urea nitrate in sulfuric acid is reported to yield the *p*-nitro derivative exclusively (44). When the para position is blocked, the meta product is obtained in excellent yield.

Reduction. Hydrogenation of aromatic amines leads to formation of cycloalkylamines, dicycloalkylamines, or both, depending on the reaction conditions and the type of catalyst used. Hydrogenation of aniline in the liquid phase at 25 MPa (250 atm) over a cobalt–alumina catalyst at 140°C yields cyclohexylamine [108-91-8] in 80° yield (45). Dicyclohexylamine [101-83-7] is produced when aniline is hydrogenated in the vapor phase over a nickel-on-pumice catalyst (46). When aniline is hydrogenated at 160–200°C in the presence of a ruthenium–palladium catalyst, supported on γ -alumina impregnated with sodium hydroxide, the product mixture is 19.3° cyclohexylamine and 80.3° dicyclohexylamine (47). Hydrogenation with a similar ruthenium–palladium catalyst supported on γ -alumina treated with manganese and chromium salts gives 91.1° cyclohexylamine and 8.8° dicyclohexylamine (48).

Addition of ammonia to the hydrogenator, 1.5 to 5 parts per 100 parts aniline, has been reported to selectively yield cyclohexylamine (49). The reduction is carried out at 160 to 180°C and 2 to 5 MPa (20 to 50 atm) with a ruthenium-on-carbon catalyst.

Cyclohexylamine is also manufactured on a commercial scale by hydrogenation of nitrobenzene without intermediate separation of aniline.

Manufacturing and Processing

The predominant process for manufacture of aniline is the catalytic reduction of nitrobenzene [98-95-3] with hydrogen. The reduction is carried out in the vapor phase (50–55) or liquid phase (56–60). A fixed-bed reactor is commonly used for the vapor-phase process and the reactor is operated under pressure. A number of catalysts have been cited and include copper, copper on silica, copper oxide, sulfides of nickel, molybdenum, tungsten, and palladium–vanadium on alumina or lithium–aluminum spinels. Catalysts cited for the liquid-phase processes include nickel, copper or cobalt supported on a suitable inert carrier, and palladium or platinum or their mixtures supported on carbon.

As an example of the vapor-phase process, nitrobenzene vapor and hydrogen are mixed and passed through a fluidized bed of copper-on-silica catalyst at 280–290°C and 500 kPa (5 atm). The reaction gas is filtered, cooled to condense aniline and water, and the excess hydrogen is recycled. The yield reported is 99.5° (42). The catalyst bed is regenerated by passing hot air through the bed to burn off the carbonaceous deposits. The aniline and water condensate are separated, and the latter is sent to the wastewater column. The organic phase is dried and the product is distilled.

Du Pont uses a liquid-phase hydrogenation process that employs a palladium –platinum-on-carbon catalyst. The process uses a plug-flow reactor that achieves essentially quantitative yields, and the product exiting the reactor is virtually free of nitrobenzene.

The old Bechamp batch process for reduction of nitrobenzene (iron–hydrochloric acid) is obsolete; however, Mobay Chemical Corporation is operating a plant using this process for production of pigment grade iron oxide as well as aniline.

The ammonolysis of phenol (61–65) is a commercial process in Japan. Aristech Chemical Corporation (formerly USS Chemical Division of USX Corporation) currently operates a plant at Haverhill, Ohio to convert phenol to aniline. The plant's design is based on Halcon's process (66). In this process, phenol is vaporized, mixed with fresh and recycled ammonia, and fed to a reactor that contains a proprietary Lewis acid catalyst. The gas leaving the reactor is fed to a distillation column to recover ammonia overhead for recycle. Aniline, water, phenol, and a small quantity of by-product diphenylamines are recovered from the bottom of the column and sent to the drying column, where water is removed.

A key feature of the Halcon process is the use of low pressure distillation (less than 80 kPa 12 psi) to break the phenol–aniline azeotrope and allow economical separation of aniline from phenol (67).

Economic Aspects

For the period 1969–1988, aniline production in the United States grew at an average annual rate of 6°. The growth pattern, however, has been cyclic. In the early 1980s aniline production declined in line with the economic recession, but recovered sharply as the economy rebounded in 1983 and 1984. Production dipped slightly in 1985, recovered in 1986, and reached an all-time high in 1988. Table 3 (68) gives the U.S. production from 1969 to 1988; Table 4 lists the manufacturers of aniline in the United States at the end of 1989.

Table 3. U.S. Production of Aniline 1969–1988^a

Year	Production, t	Year	Production, t
1969	151,494	1979	312,880
1970	176,139	1980	299,108
1971	165,981	1981	291,793
1972	185,853	1982	252,832
1973	208,542	1983	300,860
1974	249,914	1984	356,540
1975	186,701	1985	324,788
1976	246,654	1986	373,711
1977	264,932	1987	389,653
1978	272,774	1988	466,832

^a Ref. 68.

Table 4. U.S. Manufacturers of Aniline

Company	Location	Capacity, 10 ³ t
Aristech Chemical	Haverhill, Ohio	91
Du Pont	Beaumont, Tex.	113
First Chemical	Pascagoula, Miss.	136
Mobay	New Martinsville, W. Va.	18
Rubicon	Geismar, La.	172

In the 1980s manufacturing capacity for aniline underwent some major changes. It is estimated that aniline capacity utilization was about 50% of nameplate capacity when Aristech's new 91,000 t yr plant came on stream. That same year American Cyanamid closed its 23,000-t plant at Willow Island, W. Va., and withdrew from the aniline business. Mobay shut down its larger plant (45,000-t) at New Martinsville, W. Va. in 1983; and Du Pont idled its 77,000-t facility in 1984.

These reductions in capacity, coupled with the growth in aniline demand led to shortages in aniline supply in 1987 and 1988. The shortage is expected to persist into the early 1990s until new capacity comes on stream. Mobay and BASF have announced plans to build new plants (113,000 and 54,000 t, respectively), which are to start in 1992.

Aniline prices in the past have been sensitive to the balance between supply and demand in the industry and this trend is likely to continue in the next decade. List prices in the early 1980s began at \$0.97 kg, but declined to a low of \$0.64 kg as a result of industry overcapacity. By the end of 1987, prices had reached \$1.30 kg, and the price has remained firm due to strong demand for aniline.

The price of aniline is also dependent on the cost of benzene, the raw material for nitrobenzene. During the decade of the 1980s, benzene prices ranged from a low of \$0.185 L to a high of \$0.595 L. A \$0.01 L change in price of benzene is roughly equivalent to a \$0.01 kg change in the cost of aniline. At times aniline prices are stated on an "ex-benzene" basis to eliminate the effect of volatility in benzene prices on the price of the aniline sold.

Analysis and Specifications

Infrared. The infrared spectra of primary amines show a characteristic absorption doublet in the region of 3500–3300 cm⁻¹ because of the N–H stretching vibrations. Primary amines also show an N–H scissoring absorption in the range of 1650–1590 cm⁻¹. Secondary amines have a single N–H stretching absorption band in the 3500–3300 cm⁻¹ range and the bands associated with the bending vibrations are weak or absent. Tertiary amines, as expected, show no absorption in the N–H region and thus are difficult to identify by infrared spectroscopy.

Ultraviolet. Benzene has a series of relatively low intensity absorption bands in the region of 230 to 270 nm. When there is a substituent on the ring with nonbonding electrons, such as an amino group, there is a pronounced increase in the intensity of these bands and a shift to longer wavelength. Aniline shows an absorption band at 230 nm (ε 8600) and a secondary band at 280 nm (ε 1430). Protonation of the amino groups reduces these effects and the spectrum resembles that of the unsubstituted benzene.

Nuclear Magnetic Resonance. The nmr spectrum of aromatic amines shows resonance attributable to the N–H protons and the protons of any *N*-alkyl substituents that are present. The N–H protons usually absorb in the δ 3.6–4.7 range. The position of the resonance peak varies with the concentration of the amine and the nature of the solvent employed. In aromatic amines, the resonance associated with N–CH protons occurs near δ 3.0, somewhat further downfield than those in the aliphatic amines.

Gas Chromatography. Aniline and many of its derivatives are volatile and can be analyzed by gas–liquid chromatography. The method offers a rapid and accurate procedure for determination of aniline in mixtures and is the method of choice for quality control used by producers of aniline.

Other Methods. A number of chemical methods can also be used for identification of aniline (69). Table 5 gives the specifications for a typical commercial-grade aniline.

Table 5. Specifications for Commercial-Grade Aniline

Property	Value		Typical analysis
	Minimum	Maximum	
aniline, %	99.9		99.95
nitrobenzene, ppm		2.0	0.1
water, %		0.05	0.03
color ^a , APHA		100	30

^a When freshly distilled, aniline is a colorless oily liquid which darkens on exposure to light or air.

Storage and Handling

The flash point of aniline (70°C) is well above its normal storage temperature; but, aniline should be stored and used in areas with minimum fire hazard (70). Air should not be allowed to enter equipment containing aniline liquid or vapor at temperatures equal to or above its flash point.

Strong oxidizing agents, such as nitric acid, perchloric acid, or ozone may cause aniline to oxidize spontaneously. Hexachloromelamine [2428-04-8] and trichloromelamine [12379-38-3] react violently with aniline, and in confined conditions the mixtures will explode or catch fire.

Aniline is slightly corrosive to some metals. It attacks copper, brass, and other copper alloys, and use of these metals should be avoided in equipment that is used to handle aniline. For applications in which color retention is critical, the use of 400-series stainless steels is recommended.

Aniline is shipped in tank truck and tank car quantities and is classified by the U.S. Department of Transportation (DOT) as a Class B poison (UN 1547), and must carry a poison label.

Wastes contaminated with aniline may be listed as RCRA Hazardous Waste, and if disposal is necessary, the waste disposal methods used must comply with U.S. federal, state, and local water pollution regulations. The aniline content of wastes containing high concentrations of aniline can be recovered by conventional distillation. Biological disposal of dilute aqueous aniline waste streams is feasible if the bacteria are acclimated to aniline. Aniline has a 5-day BOD of 1.89 g of oxygen per gram of aniline.

Aniline can be safely incinerated in properly designed facilities. It should be mixed with other combustibles such as No. 2 fuel oil to ensure that sufficient heating values are available for complete combustion of aniline to carbon dioxide, water, and various oxides of nitrogen. Abatement of nitrogen oxides may be required to comply with air pollution standards of the region.

Health Hazards and Safety Precautions

Aniline is highly toxic and may be fatal if swallowed, inhaled, or absorbed through the skin. Aniline vapor is mildly irritating to the eye, and in liquid form it can be a severe eye irritant and cause corneal damage. The first sign of aniline poisoning is cyanosis, a bluish tinge to the lips and tongue, caused by conversion of the blood hemoglobin to methemoglobin. As methemoglobin concentration of the blood rises above a certain level, death may result from anoxia.

The U.S. Department of Labor (OSHA) has ruled that an employee's exposure to aniline in an 8-h work shift of a 40-h work week shall not exceed an 8-h time-weighted average (TWA) of 5 ppm vapor in air. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a

threshold limit value (TLV) of 2 ppm aniline vapor in air, TWA for an 8-h work day (71).

Based on tests with laboratory animals, aniline may cause cancer. The National Cancer Institute (NCI) and the Chemical Industry Institute of Toxicology (CIIT) conducted lifetime rodent feeding studies, and both studies found tumors of the spleen at high dosage (100 –300 mg kg per day of aniline chloride). CIIT found no tumors at the 10–30 mg kg per day feeding rates. The latter value is equivalent to a human 8-h inhalation level of 17–50 ppm aniline vapor. In a short term (10-d) inhalation toxicity test by Du Pont, a no-effect level of 17 ppm aniline vapor was found for rats. At high levels (47–87 ppm), there were blood-related effects which were largely reversible within a 13-d recovery period (70).

In view of the above, aniline should be handled in areas with adequate ventilation and skin exposure should be avoided by wearing the proper safety equipment. Recommended personal protective equipment includes hard hat with brim, chemical safety goggles, full length face shield, rubber gauntlet gloves, rubber apron, and rubber safety shoes or rubber boots worn over leather shoes.

Uses

The major uses of aniline are in the manufacture of polymers, rubber, agricultural chemicals, dyes and pigments, pharmaceuticals, and photographic chemicals. Approximately 67° of the world production of aniline is used in the manufacture of rigid polyurethanes and reaction-injection-molded (RIM) parts for the construction, automotive, and durable goods industries.

Rubber chemicals, primarily antioxidants (qv), stabilizers, and antiozonants (qv), account for 12° of the demand for aniline worldwide. Important agricultural uses for aniline derivatives include fungicides, insecticides, animal repellents, and defoliants. It is estimated that less than 5° of the aniline produced in 1988 was consumed for agricultural chemicals.

Aniline demand in the United States is expected to grow at an average annual rate of 4 to 6° in the 1990s. The demand for MDI, the fastest growing segment, is forecast to grow at 5 to 8° annual rate by its major producers. The growth is largely due to the trend towards the use of more plastic, and lighter, parts in new automobiles and durable goods.

A potential downside factor in the projected demand for MDI is the global regulation of the release of chlorofluorocarbons (CFCs) to the atmosphere. CFCs are used as blowing agents in production of polyurethane rigid foams. Therefore, alternate materials such as polystyrene rigid foams (that use hydrocarbon blowing agents) may replace the polyurethane foams in some applications.

Other aniline uses are projected to grow at rates ranging from 0 to 4° annually, with agricultural chemicals at the low end and rubber chemicals at the upper end of this range.

Derivatives

Most derivatives of aniline are not obtained from aniline itself, but are prepared by hydrogenation of their nitroaromatic precursors. The exceptions, for example, *N*-alkylanilines, *N*-arylanilines, sulfonated anilines, or the *N*-acyl derivatives, can be prepared from aniline and have been discussed. Nitroanilines are usually prepared by ammonolysis of the corresponding chloronitrobenzene. Special isolation methods may be required for some derivatives if the boiling points are close and separation by distillation is not feasible. Table 6 lists some of the derivatives of aniline that are produced commercially.

Table 6. Aniline Derivatives

Class of compound and common name	Molecular formula	CAS Registry Number	Condensed structural formula	Appearance	Melting point, °C	Boiling point, °C	Commercial derivatives and uses
salts							
aniline hydrochloride	C ₆ H ₇ N·ClH	[142-04-1]	C ₆ H ₅ NH ₂ ·HCl	white solid	198	245	Aniline black
aniline sulfate	C ₆ H ₇ N·1/2H ₂ O ₄ S	[542-16-5]	(C ₆ H ₅ NH ₂) ₂ ·H ₂ SO ₄	white crystals			sulfanilic acid
<i>N</i> -alkyl, <i>N</i> -aryl <i>N</i> -methylaniline	C ₇ H ₉ N	[100-61-8]	C ₆ H ₅ NHCH ₃	yellow liquid	57	194.6	
<i>N,N</i> -dimethylaniline	C ₈ H ₁₁ N	[121-69-7]	C ₆ H ₅ N(CH ₃) ₂	yellow liquid (darkens in air)	2	193–194	vanillin; Michler's ketone; alkylating agents; dyes
<i>N</i> -ethylaniline	C ₈ H ₁₁ N	[103-69-5]	C ₆ H ₅ NHC ₂ H ₅	colorless liquid (darkens in air)	63.5	204.7	explosive stabilizer; dyes
<i>N,N</i> -diethylaniline	C ₁₀ H ₁₅ N	[91-66-7]	C ₆ H ₅ N(C ₂ H ₅) ₂	pale yellow liquid	38.8	215–216	alkylating agent
<i>N</i> -benzyl- <i>N</i> -ethylaniline	C ₁₅ H ₁₇ N	[92-59-1]	C ₆ H ₅ N(C ₂ H ₅)CH ₂ C ₆ H ₅	light yellow oil		314	triphenylmethane dyes
diphenylamine	C ₁₂ H ₁₁ N	[122-39-4]	C ₆ H ₅ NHC ₆ H ₅	white crystals, floral odor	54–55	302	rubber antioxidants; phenothiazine
<i>C</i> -alkyl <i>o</i> -toluidine	C ₇ H ₉ N	[95-53-4]	H ₃ CC ₆ H ₄ NH ₂	yellow liquid (darkens in air)		200–202	triphenylmethane dyes; safranine colors
<i>m</i> -toluidine		[108-44-1]		colorless liquid	30.4	203–204	dyes
<i>p</i> -toluidine		[106-49-0]		white crystals	44–45	200–201	Basic Red 9; Acid Green 25
2,3-xylidine	C ₈ H ₁₁ N	[87-59-2]	(H ₃ C) ₂ C ₆ H ₃ NH ₂	liquid	< 15	221–222	
2,4-xylidine		[95-68-1]		liquid	16	214	Solvent Orange 7; Direct Violet 14
2,5-xylidine		[97-78-3]		oily liquid	15.5	213.5	<i>p</i> -xyloquinone; Red 26; Direct Violet 7
2,6-xylidine		[87-62-7]		colorless liquid	11–12	216–217	formerly in dyes
3,4-xylidine		[95-64-7]		solid	51	226	synthetic riboflavin
3,5-xylidine		[108-69-0]		oil	9.8	220–221	azo dyes
<i>C</i> -alkoxy <i>o</i> -anisidine	C ₇ H ₉ NO	[90-04-0]	H ₃ COC ₆ H ₄ NH ₂	yellow liquid (darkens in air)	5–6	225	guaiacol synthesis; Direct Red 24; Solvent

<i>m</i> -anisidine		[536-90-3 /		oily liquid	1–1	251	Red 1
<i>p</i> -anisidine		[104-94-9 /		white solid	57	243	dyes
<i>o</i> -phenetidine	C ₈ H ₁₁ NO	[94-70-2]	H ₅ C ₂ OC ₆ H ₄ NH ₂	oily liquid	< 21	231–233	dyes
<i>p</i> -phenetidine		[156-43-4 /		liquid (darkens in air)	3–4	254–255	phenacetin; phenocoll; rubber antioxidant; dyes
<i>p</i> -cresidine	C ₈ H ₁₁ NO	[120-71-8 /	H ₃ CO(CH ₃)C ₆ H ₃ NH ₂	white crystals	52–54	235	FD&C Red 40
<i>N</i> -acyl formanilide	C ₇ H ₇ NO	[103-70-8 /	HCONHC ₆ H ₅	white crystals	50	271	analgesic and antipyretic
acetanilide	C ₈ H ₉ NO	[103-84-4 /	CH ₃ CONHC ₆ H ₅	colorless crystals	114.3	304	intermediate for sulfa drugs; hydrogen peroxide stabilizer; azo dyes
acetoacetanilide	C ₁₀ H ₁₁ NO ₂	[102-01-2 /	CH ₃ COCH ₂ CONHC ₆ H ₅	white crystals	86		intermediate for pyrazolones and pyrimidines; Hansa yellows; benzidine yellow pigments
chloroanilines							
2-chloroaniline	C H ClN	[95-51-2]	ClC ₆ H ₄ NH ₂	colorless liquid	14	208–210	dyes
3-chloroaniline		[108-42-9 /		colorless liquid	10	230–231	dyes
4-chloroaniline		[106-47-8 /		colorless liquid	72.5	232	azoic dye coupling
2,5-dichloroaniline	C H ₅ Cl ₂ N	[95-82-9]	Cl ₂ C ₆ H ₃ NH ₂	needle crystals	51	251	Component 10 and 15 dyes
3,4-dichloroaniline		[95-76-1]		white crystals	71.5	272	herbicides; dyes
sulfonated anilines							
orthanilic acid	C H ₇ NO ₃ S	[88-21-1]	H ₂ NC ₆ H ₄ SO ₃ H	colorless crystals	>320 dec		dyes
metanilic acid		[121-47-1 /		white crystals	dec		Acid Yellow 36, Direct Yellow 44 dyes
sulfanilic acid		[121-57-3 /		white crystals	288		Acid Orange 1; Food Yellow 3 dyes
nitroanilines							
2-nitroaniline	C H N ₂ O ₂	[88-74-4]	O ₂ NC ₆ H ₄ NH ₂	golden crystals	71–72	284	Vat Orange 7 and Red 14 dyes
3-nitroaniline		[99-09-2]		yellow crystals	114	305–307 dec	synthetic intermediate; dyes
4-nitroaniline		[100-01-6 /		pale yellow crystals	148–149	332	dyes; intermediate for 1,4-phenylenediamine
2,4-dinitroaniline	C H ₅ N ₃ O ₄	[97-02-9]	(O ₂ N) ₂ C ₆ H ₃ NH ₂	yellow crystals	187–188		Pigment Orange 5; dyes
2,4,6-trinitroaniline	C H ₄ N ₄ O	[489-98-5 /	(O ₂ N) ₃ C ₆ H ₂ NH ₂	yellow solid	192–195	explodes	explosives; detonators

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DIAMINOTOLUENES

Toluenediamine (diaminotoluene, *m*-TDA) is an important industrial chemical intermediate; it is produced in the largest volume of any arylamine and is the lowest priced diamine (1). Worldwide production in 1991 was estimated at 6.9 × 10⁵ metric tons; the United States accounts for about 45% of the volume. TDA producers in the United States include Air Products and Chemicals Corporation (merchant only), Mobay Corporation (Bayer USA), BASF Corporation, Olin Corporation, Dow Chemical USA, and Rubicon Corporation (ICI). The principal use for TDA is in the manufacture of toluenediisocyanate (TDI), the predominant diisocyanate in the flexible foams and elastomers industries. Reaction with phosgene converts TDA to TDI which undergoes reaction with a polyol to give the corresponding polyurethane. The isomer *ortho*-toluenediamine is also produced in commercial quantities in the United States and is supplied for producing polytriazoles and polyols. Available volume of *o*-TDA is limited by the isomer distribution of the precursor nitration reaction.

Physical Properties

Although all six possible toluenediamine isomers are made in the commercial synthesis, only two products are available commercially. The properties of the individual isomers are summarized in Table 1. Specifications for the commercial products, named by the relative position of the predominant groups, along with some physical properties, are shown in Table 2.

Table 1. Physical Properties of the Toluendiamine Isomers^a

Diaminotoluene isomers	CAS Registry Number	Melting point, °C	Boiling point, °C	Vapor pressure, kPa ^b (at °C)
2,3	[2687-25-4]	63–64	255	1.20 (150) 1.87 (160) 2.67 (180)
2,4	[95-80-7]	99	292	1.47 (150) 2.27 (160) 4.80 (180)
2,5	[95-70-5]	64	273–274	
2,6	[823-40-5]	106		2.13 (150) 3.33 (160) 7.60 (180)
3,4	[496-72-0]	89–90	265 (subl)	
3,5	[108-71-4]	<0	283–285	

^a Ref. 2

^b To convert kPa to mm Hg, multiply by 7.5

Table 2. Specifications and Physical Properties of Commercial Toluenediamines

Property	Specifications, wt %	
	<i>m</i> -TDA ^a	<i>o</i> -TDA ^b
<i>m</i> -TDA, purity normalized isomer ratio	99.0 min	
2,4 [95-80-7]	79–81	
2,6 [823-40-5]	19–21	
<i>o</i> -TDA, (2,3 [2687-25-4] and 3,4 [496-72-0])	0.3 max	99.2 min
<i>p</i> -isomers (2,5 and 3,5)	1.0 max	
meta- plus para-isomer content		0.3 max
nitro bodies as DNT	0.03 max	
moisture	0.1 max	0.5 max
toluidines	0.05 max	0.3 max
molecular formula	C ₇ H ₁₀ N ₂	C ₇ H ₁₀ N ₂
molecular weight	122.17	122.17
physical appearance	light yellow to tan solid ^c	light gray to purple solid ^a
boiling point at 101.3 kPa ^d , °C	283	265 (3,4 TDA) 255 (2,3 TDA)
viscosity at 100°C, mPa·s(cP)	5	5
density, g /mL	1.041 (105°C)	1.045 (100°C)
melting range, °C	88–96	61–92
flash point, open cup, °C		>110
heat of vaporization, kJ /mol ^e	61.3 (2,4 TDA)	68.0
heat of fusion, kJ /mol ^e	19.9 (2,4 TDA)	19.8
specific heat at 150°C, kJ / (kg·K) ^e	2.53	2.53
vapor pressure at 100°C, Pa ^d	<133	266

^a Ref. 3.

^b Ref. 4.

^c Tends to darken on storage and exposure to air.

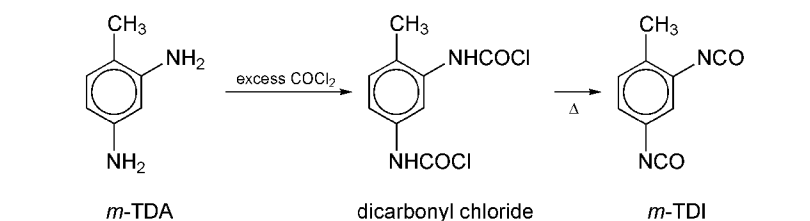
^d To convert kPa to mm Hg, multiply by 7.5.

^e To convert kJ to kcal, divide by 4.184.

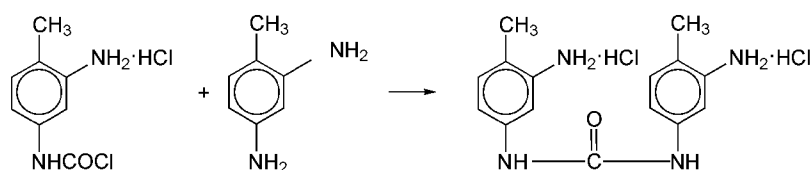
Reactions

The aromatic toluenediamines undergo typical amine reactions. The general chemistry is similar to that of the phenylenediamines or the cyclohexanediamines except that the aromatic diamine is a weaker base than its cycloaliphatic counterpart. Only reactions of industrial importance particular to commercial toluenediamines are discussed below.

Phosgenation. The most important reaction of *m*-toluenediamine is with phosgene [75-44-5] to give toluene diisocyanate TDI (see ISOCYANATES, ORGANIC).

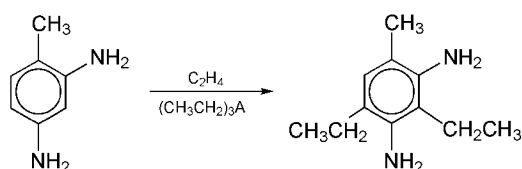


To avoid partially phosgenated intermediates and coupling reactions such as

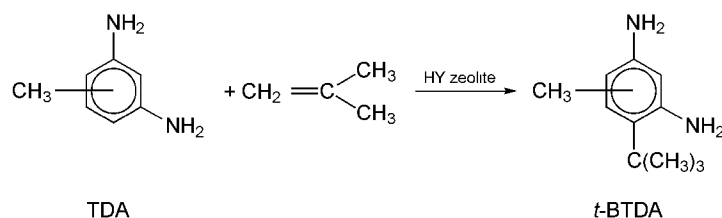


the procedure for making TDI from TDA involves a cold phosgenation in an inert solvent with excess phosgene, followed by heating with excess phosgene. By-products are substituted ureas and benzimidazolone formed from ortho-substituted diamines and phosgene. The by-products are tarry dark materials which are difficult to remove and may lead to environmental problems. Therefore, the presence of ortho-diamine results in lower yield in the manufacture of TDI and a very objectionable impurity in the final product.

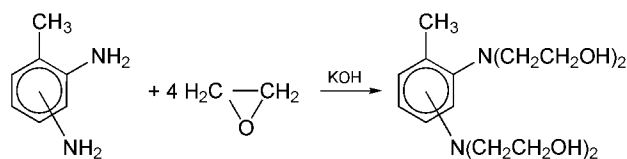
Ring Alkylation. Ortho alkylation of TDA has taken on increasing commercial importance. Ortho ethylation, the first commercial process, is carried out (5–8) using an alkyl aluminum halide or an aluminum anilide. The alkylation rate decreases for higher alkenes (1).



Acid catalysis using strong acid catalysts, especially zeolites which enhance selectivity because of pore size restrictions, has been used for a variety of alkenes and dienes (9–11). *t*-Butyltoluenediamine [106398-83-8] (*t*-BTDA) ($\text{C}_{11}\text{H}_{18}\text{N}_2$) is available on a semicommercial basis (12).

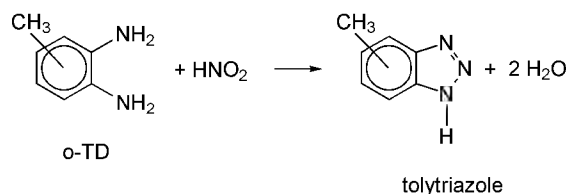


Alkoxylation. Ethoxylation of toluenediamines proceeds easily. Typical conditions are 90 to 120°C at pressures up to 500 kPa (72.5 psi) using a basic catalyst, eg, potassium hydroxide (13).



Many specific reaction conditions using other alkylene oxides (14) or combinations of alkylene oxides (15) may be found in the patent literature.

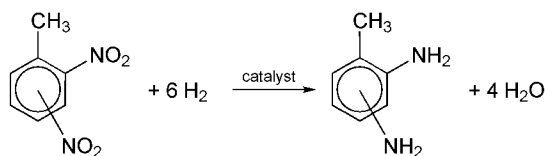
Diazotization. The general reactions of *o*-diamines with an alkali nitrite and an acid with subsequent ring closure are well known.



Several process improvements using aqueous solution at elevated temperatures (350°C) and pressure (16) or using an organic solvent and an acid at milder temperatures (<80°C) have been described for *o*-TD (17).

Manufacture

Dinitrotoluenes can be catalytically hydrogenated to toluenediamines under a wide variety of temperatures, pressures, and solvents; the catalyst can be supported noble metal, eg, Pd/C or nickel, either supported or Raney type. The reduction requires six moles of hydrogen per mole of DNT and produces four moles of water.



Since nitroarenes are reported to be catalyst poisons (18), the concentration of DNT in the reaction medium is kept as low as is practical with regard to production goals and catalyst usage. The published kinetic studies are of little industrial value since they describe batch processes with high DNT: catalyst ratios (18–21). The effects of important process variables, such as temperature and pressure, can only be inferred from descriptions in the patent literature.

Processes. Toluene is nitrated in two stages. Mononitration occurs in mixed acid, 30% HNO_3 and 55% H_2SO_4 , at 30–70°C in a series of continuous stirred-tank reactors. Heat is liberated and must be removed. The isomer distribution is approximately 58% *o*-nitrotoluene, 38% *p*-nitrotoluene, and 4% *m*-nitrotoluene (Fig. 1).

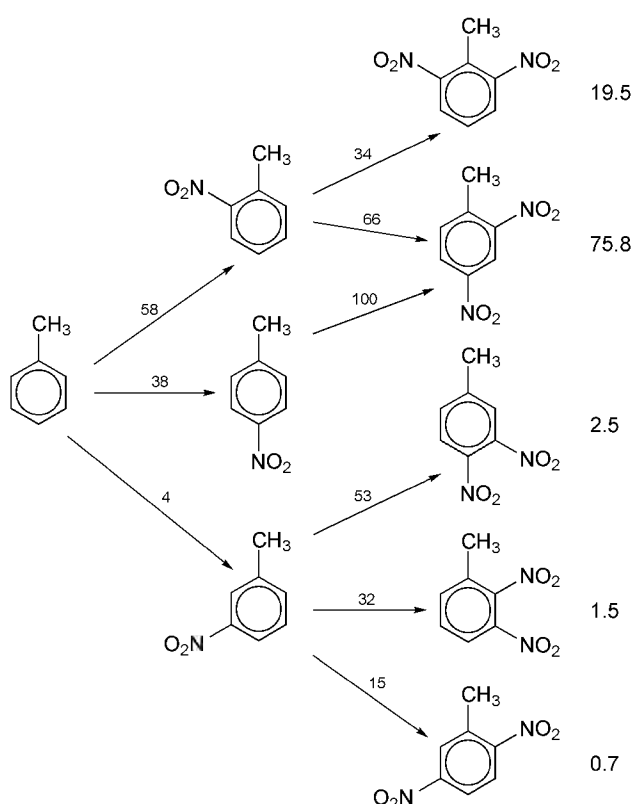


Fig. 1. Nitration of toluene, percent distribution.

The mononitrotoluenes ($\text{C}_7\text{H}_7\text{NO}_2$) are then nitrated in a second set of continuous reactors with a stronger mixed acid (30% HNO_3 and 63% H_2SO_4) to give dinitrotoluenes ($\text{C}_7\text{H}_5\text{N}_2\text{O}_4$): 75.8% 2,4-DNT, 19.5% 2,6-DNT, 0.7% 2,5-DNT, 1.5% 2,3-DNT, and 2.5% 3,4-DNT; the 3,5 isomer is undetectable. In Figure 1, the *ortho* isomers, 2,3-DNT and 3,4-DNT, are derived from nitration of *m*-nitrotoluene; these eventually become undesired by-products in the manufacture of TDI. Patents for the catalytic hydrogenation of DNT differ in catalyst, temperature pressure, solvent, and type of reactor. Examples of the main variations in the technology are described in the following.

Hydrogenation with a noble metal catalyst and external filter is described in a series of patents assigned to the Du Pont Company (22–25). DNT is introduced into a continuous stirred tank reactor with Pd/C catalyst and hydrogen at 550–690 kPa (80–100 psi) at 70–80°C. The DNT content must be kept low (about 0.5%) to keep yields high (99%). One part of the product stream is recycled to the reactor to act as the reaction solvent; the remainder is filtered to remove catalyst and then purified. The use of a precious metal catalyst allows mild operating conditions and provides high reaction yield. The high cost of the catalyst requires near perfect catalyst recovery. Energy recovery at the low operating temperatures is difficult.

A process based on a nickel catalyst, either supported or Raney type, is described in Olin Mathieson patents (26,27). The reduction is carried out in a continuous stirred tank reactor with a concentric filter element built into the reactor so that the catalyst remains in the reaction zone. Methanol is used as a solvent. Reaction conditions are 2.4–3.5 MPa (350–500 psi), 120–140°C. Keeping the catalyst inside the reactor increases catalyst lifetime by maintaining a hydrogen atmosphere on its surface at all times and minimizes handling losses. Periodic cleaning of the filter element is required.

Yield for the process at low catalyst loading is 95%. *N*-Methyl-toluenediamine, one of the reaction by-products, represents not only a reduction in yield, but also a highly objectionable impurity in the manufacture of toluene diisocyanate. Low concentrations of CO (0.3–6% volume) control this side reaction.

Another nickel catalyzed process is described in a Tolochimie patent (28). Reaction conditions claimed are 1–2.4 MPa (150–350 psi) at 100°C minimum. The combination continuous stirred reactor and gravity decanter uses density-driven circulation between the two vessels to recirculate the catalyst to the reaction zone without the use of filters or pumps. Yield and catalyst usage can be controlled by varying the feed rates.

Bayer AG holds a number of patents (29–32) covering the use of a bubble-tube reactor for carrying out the reduction. DNT along with recycled reactor mixture, solvent, catalyst, and hydrogen are fed upwards through a column. A wide variety of catalysts are claimed as suitable, both supported precious metal and Raney metals. Catalyst must be in a finely divided form and is held in suspension by excess hydrogen flow. Reaction pressure is given as between 4–20 MPa (600–3000 psi) at a temperature of 140–250°C. Several interesting process modifications are claimed in these patents including generation of steam from reactor cooling, and high pressure crossflow catalyst filtration.

The use of fixed bed catalysts is described in several patents (33–37). Methods of operation include upflow, trickle bed, and even vapor phase. Typically, a large volume of solvent is used to moderate the temperature rise associated with the high heat of reaction for nitro group reduction.

Subsequent separation of this solvent imposes substantial capital and operating cost penalties. A Bayer AG patent (37) claims use of a solvent in which DNT is soluble, but in which the TDA is practically insoluble. This allows separation and recycle of the solvent to the reactor without any distillation process.

Purification after catalyst removal requires separation of the TDA from the water of reaction and tars, and, depending upon the procedure used in preparing TDI, from the ortho-substituted diamines. The general scheme for the purification shown in Figure 2 is based on Allied Chemical patents (38,39). The first column is an atmospheric column which removes water of reaction and any toluidine formed. Then the crude *m*-toluenediamine (*m*-TDA) is distilled under reduced pressure, 1.3–2.6 kPa (10–20 mm Hg) recovering the *o*-toluenediamine (*o*-TD) overhead. The TDA is taken from the bottom of the first vacuum column and redistilled to remove the heavy products. This process gives more than a 99% TDA yield. Although vacuum distillation would appear to be the most economical purification of TDA, several other methods for removing the *o*-TD have been described (40–44). Most of these are based on formation of cyclic products (eg, methylbenzimidazolinones and Ni(II) complex salts) which can be easily separated from the TDA. Cost of reactants and the need for further purification limits the usefulness of these methods.

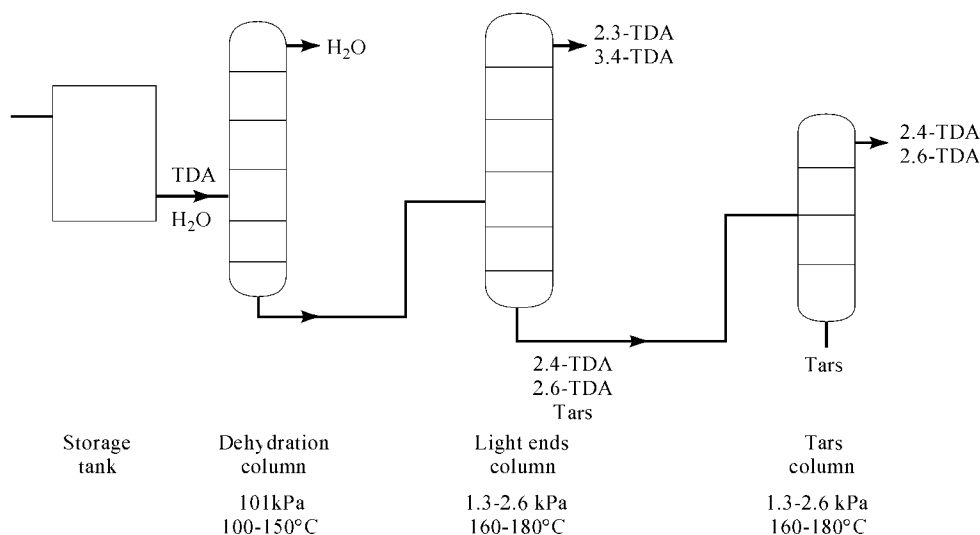


Fig. 2. Purification scheme for crude toluenediamine (TDA).

Toxicity

Toluenediamine is classed as toxic. The oral LD₅₀ for animals is between 270–350 mg/kg body weight (45). TDA is readily absorbed through the skin and this is the major route of human exposure. Several studies have shown the 2,4 isomer of TDA to be carcinogenic for rats and mice, but tests on the 2,5 and 2,6 isomers were not positive. All three of the isomers have been shown to be mutagenic (45). Results of limited studies on the reproductive hazards for male workers are equivocal, but animal experiments have shown TDA to cause adverse reproductive effects (45).

Uses

Only a few commercial uses for TDA per se have been found. In epoxy curing applications, 2,4-TDA has been used as a component of a eutectic mixture with short chain aliphatic glycidal ether resins (46) as well as by itself (46,47); TDA (46) and single isomers (47) are also used as amine curatives. TDA can be used as a chain extender in polyurethanes (48,49). TDA is cited as a monomer in making aromatic polymers with unique properties, eg, amorphous polyamides (50), powdered polyamides (51), and low melting, wholly aromatic polyamides (52).

Almost all TDA use is as a chemical intermediate, mostly in polyurethanes. Toluenediamine derivatives are found as all three components of urethanes: isocyanates, chain extenders, and polyols (see ISOCYANATES, ORGANIC; URETHANE POLYMERS).

Almost all TDA derived chain extenders are made through ortho-alkylation. Diethyltoluenediamine (DETDA) (C₁₁H₁₈N₂) (53), with a market of about 33,000 t, is the most common. Many uses for *t*-BTDA have been cited (1,12). Both DETDA and *t*-BTDA are especially useful in RIM applications (49,53–55). Di(methylthio)-TDA, made by dithioalkylation of TDA, is used in cast urethanes and with other TDI prepolymers (56). Styrenic alkylation products of TDA are said to be useful, eg, as in the formation of novel polyurethane–polyurea polymers (57,58). Progress in understanding aromatic diamine structure–activity relationships for polyurethane chain extenders should allow progress in developing new materials (59). Chlorinated TDA is used in polyurethane–polyurea polymers of low hysteresis (48) and in reinforced polyurethane tires (60). The chloro-TDA is made by hydrolysis of chloro-TDI, derived from TDA (61).

TDA-derived polyols are made by alkoxylation. Polypropylene oxide adducts of TDA (14) and TDA-initiated polyether polyols (13,15) are used in rigid polyurethane foams and continue to be included in new formulations (62) as well as older applications.

Alkylated and alkenated toluenediamines are used as antioxidants (qv) in oils and elastomers (10,53,63–65), as chemical intermediates for polyamides, polyimides, and polyesterimides (53,1) and as epoxy curatives (53,58,66) (see EPOXY RESINS).

The most significant commercial use of *o*-TDA is in the manufacture of polytriazoles. Polytriazoles are used as corrosion inhibitors, chemical intermediates, photographic chemicals, and catalysts (16). Other uses for *o*-TDA include polyols (13,54) and antioxidants (54).

Toluenediamine derivatives are used as dyes (67,68) (see also AZO DYES; HAIR PREPARATIONS; AMINES, AROMATIC (PHENYLENEDIAMINES)). A variety of other hard-to-classify uses are found. Improved fatigue resistance and dyeability are claimed for a fiber prepared from toluene-2,4-diamine and various diacids (69). An anhydride reacts with a formaldehyde–toluenediamine copolymer to give an impact-resistant resin (70). A fluorinated polyamide elastomer containing TDA has been described (71). The synthesis of benzimidazolethiols, useful as antioxidants, from the by-product *o*-TDA obtained during TDI manufacture, has been described (72). Treatment of polyester fibers with toluenediamines improves the adhesion of elastomers (73,74). Uses as specific stabilizers for fungicides have been patented (75,76). Hydraulic fluids have been synthesized from toluene-2,4-diamine and alkylene oxides, preferably glycidol (77). Diamines can be used as sensitizers for explosive compositions (78,79).

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DIARYLAMINES

Diarylamines are compounds that have two aromatic groups and one hydrogen atom attached to nitrogen. Diphenylamine (DPA), or *N*-phenylbenzenamine [122-39-4], is the most commercially significant diarylamine. It was first prepared by Hofmann in 1863 by destructive distillation of triphenylmethane dyes. Today, it is manufactured by heating aniline by itself, or with phenol, and with an acid catalyst at high temperatures. It is used as a stabilizer for nitrocellulose propellants. When alkylated, diphenylamine finds its largest application as an antioxidant and stabilizer for oils, greases, polymers, and elastomers. Diarylamines that contain other functional groups, such as hydroxyl or amino, are useful dye intermediates, antiozonants, hair dyes, and color photography intermediates.

Physical Properties

Selected physical properties for representative diarylamines are given in Table 1. The solubility of DPA in water (1) is given by:

log*c* = 1.5786 - 1571 / *T* °C

where *c* is the concentration of DPA in mol / L. The solubility at 10, 15, 20, 25, and 30°C is 1.06, 1.35, 1.75, 2.11, and 2.61 × 10⁻⁴ mol / L, respectively.

Table 1. Physical Properties of Diarylamines

Diarylamine	CAS Registry Number	Formula	Mp, °C	Bp, °C ^a
diphenylamine	[122-39-4]	C ₁₂ H ₁₁ N	53	302
2-methyldiphenylamine	[1205-39-6]	C ₁₃ H ₁₃ N	41	175(2.93)
3-methyldiphenylamine	[1205-64-7]	C ₁₃ H ₁₃ N	27.5	
4-methyldiphenylamine	[620-84-8]	C ₁₃ H ₁₃ N	88	
4-(1,1-dimethylethyl) diphenylamine	[4496-49-5]	C ₁₁ H ₁₉ N	67	139(0.05)
4-octyldiphenylamine	[4175-37-5]	C ₂₀ H ₂₇ N	48	152(0.03)
4,4'-bis(1,1-dimethylethyl) diphenylamine	[4627-22-9]	C ₂₀ H ₂₇ N	110	
4,4'-bis(1-phenylethyl) diphenylamine	[60160-25-0]	C ₂₈ H ₂₇ N		
4,4'-bis(1-methyl- 1-phenylethyl)diphenylamine	[10081-67-1]	C ₃₀ H ₃₁ N	101	
4,4'-dioctyldiphenylamine	[101-67-7]	C ₂₈ H ₄₃ N	102	
2,2'-diethyldiphenylamine	[64653-59-4]	C ₁₁ H ₁₉ N		
2,2'-bis(1-methylethyl) diphenylamine	[64653-45-8]	C ₁₈ H ₂₃ N		
2,4,4'-tris(1-methyl- 1-phenylethyl)diphenylamine	[17419-19-1]	C ₃₉ H ₄₁ N	122	
4-hydroxydiphenylamine	[122-37-2]	C ₁₂ H ₁₁ NO	73	200(1.33)
4,4'-dimethoxydiphenylamine	[101-70-2]	C ₁₄ H ₁₅ NO ₂	103	
<i>N</i> -phenyl- 1-naphthylamine	[90-30-2]	C ₁₁ H ₁₃ N	62	244(16)
<i>N</i> -[4-(1-methyl- 1-phenylethyl) phenyl]- 1-naphthylamine	[17418-49-4]	C ₂₅ H ₂₃ N	92	
<i>N</i> -phenyl-2-naphthylamine	[135-88-6]	C ₁₁ H ₁₃ N	108	395
<i>N</i> -[4-(1-methyl- 1-phenylethyl) phenyl]- 1-(1-methyl- 1-phenylethyl)-2-naphthylamine	[17418-51-8]	C ₃₄ H ₃₃ N	122	
di-6-chrysenylamine	[64743-18-6]	C ₃₁ H ₂₃ N	314	
<i>N</i> -nitrosodiphenylamine	[86-30-6]	C ₁₂ H ₁₀ N ₂ O	68	
<i>N,N'</i> -diphenyl- <i>p</i> -phenylenediamine	[74-31-7]	C ₁₈ H ₁₁ N ₂	152	200(0.07)
<i>N,N'</i> -di-2-naphthyl- <i>p</i> -phenylenediamine	[93-46-9]	C ₂₂ H ₂₀ N ₂	234	
9 <i>H</i> -carbazole	[86-74-8]	C ₁₂ H ₉ N	245	
9,10-dihydro-9,9-dimethyl acridine	[6267-02-3]	C ₁₅ H ₁₅ N	137	
10 <i>H</i> -phenothiazine	[92-84-2]	C ₁₂ H ₉ NS	193	
8-octyl- 10 <i>H</i> -phenothiazine	^b	C ₂₀ H ₂₁ NS	118	

^a At 101.3 kPa unless otherwise indicated in kPa in parentheses. To convert kPa to mm Hg, multiply by 7.5.

^b CAS Registry Number not assigned.

Diphenylamine is a weak base, *K*_b = 9 × 10⁻⁴. Dilute acids are used to separate DPA from primary aromatic amines, such as aniline, *K*_b = 4 × 10⁻¹⁰. Diphenylamine hydrochloride [537-67-7] is stable in the presence of 7.5% or stronger hydrochloric acid, but dissociates in more dilute solutions.

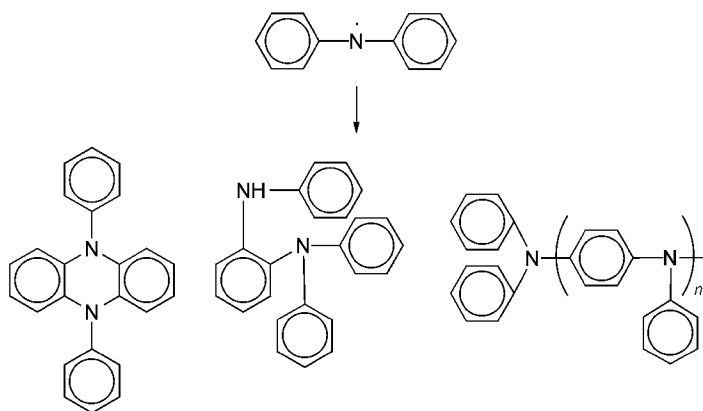
Reactions

C-Alkylation. Since para-alkylated derivatives of DPA are widely used in large volumes as antioxidants (qv), the most important reaction of DPA is the acid catalyzed reaction with olefins (2,3). Alkylation is carried out by adding the olefin to a mixture of DPA and an acid catalyst, such as AlCl₃ or an acidic clay, at 120–140°C. Most low cost olefins, mixtures of olefins, and dienes have been used in reactions with DPA. The common commercial alkylated diphenylamines are derived from isobutylene, diisobutylene, styrene, or α-methylstyrene. Diisobutylene primarily produces mono- and di-para tertiary octyl derivatives since steric hindrance significantly slows the alkylation at the ortho position. Thus, only a small amount of tri-substituted product is obtained. Less hindered olefins, eg, styrene, which give a secondary alkyl group, produce proportionally larger amounts of tri and tetra substituted DPA. Alkylation with various diolefins leads to the formation of higher molecular weight, polymeric products (4).

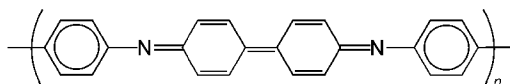
Acetone also reacts with diphenylamine, in the presence of acid, to form a variety of condition-dependent products (5). Excess amine and a small amount of strong acid catalyst at 100–150°C give 2,2-[4,4'-(dianilino)diphenyl]-propane [2980-26-9] (6). With a large amount of hydrochloric acid at 250°C in the presence of excess diphenylamine, the main product is 9,9-dimethylacridan [6267-02-3].

Diphenylamine can be alkylated exclusively in the ortho positions by reacting with an olefin in the presence of aluminum diphenylamide (7), which can be readily obtained by heating DPA with powdered aluminum, or more easily by treating sodium diphenylamide with AlCl_3 . Ethylene is more reactive than propylene, which in turn is more reactive than isobutylene. For a typical reaction, a small amount of the amide is generated in a DPA melt and ethylene is introduced under pressure (5–30 MPa) at 200–400°C. The absorption of ethylene stops after about 30 min and 2,2'-diethyldiphenylamine is obtained in 95% yield. With propylene only a 25% yield of the 2,2'-diisopropyldiphenylamine is obtained.

Oxidation. Diarylamines are widely used as antioxidants primarily because they react with and destroy chain propagating peroxy radicals. The first product formed is a long-lived but generally not isolable aminyl radical (8). These radicals can react with other peroxy radicals or couple through the nitrogens, or at the ortho or para positions of the aromatic rings, to give dimers and high molecular weight oligomers such as the following (9).



Thus, *N,N,N',N'*-tetraphenylhydrazine [632-52-0], 5,10-dihydro-5,10-diphenylphenazine [3665-72-3], and *N,N,N'*-triphenyl-1,2-benzenediamine [29325-54-0] are oxidation products of DPA. The permanent stain caused by these compounds is in part due to the formation of the following highly conjugated, polymeric products which are insoluble:



For antioxidant activity, the reaction of aminyl radicals with peroxy radicals is very beneficial. The nitroxyl radicals formed in this reaction are extremely effective oxidation inhibitors. Nitroxides function by trapping chain-propagating alkyl radicals to give hydroxylamine ethers. These ethers, in turn, quench chain propagating peroxy radicals and in the process regenerate the original nitroxides. The cyclic nature of this process accounts for the superlative antioxidant activity of nitroxides (see ANTIOXIDANTS). Thus, antioxidant activity improves with an increase in stability of the aminyl and nitroxyl radicals. Consequently, commercial DPA antioxidants are alkylated in the ortho and para positions to prevent undesirable coupling reactions.

Although aminyl radicals are stable towards oxygen, they can oxidize other aromatic amines, phenols and thiols (10), and regenerate the diarylamine. Thus, mixtures of phenols and diarylamines frequently show better antioxidant activity than either one alone. This is called synergism.

Nitroxyl radicals of diarylamines can also be obtained on oxidation with hydrogen peroxide in the presence of vanadium ions. Resonance helps stabilize these radicals. For example, the nitroxide from 4,4'-dimethoxydiphenylamine [63619-50-1] is stable for years, whereas the radical from the unsubstituted diphenylamine cannot be isolated. Substitution in the ortho and para positions also increases the stabilities of these nitroxides by inhibiting coupling reactions at these sites. However, they are not as stable as the sterically hindered tetramethylpiperidyl radical.

Miscellaneous Reactions. The *N*-hydrogen atom of diphenylamine is reactive and readily replaced by deuterium by treating with $\text{C}_2\text{H}_5\text{OD}$. The addition of acid catalyzes the exchange of the hydrogen atoms on the ring system (11).

Electrophilic substitution reactions of diarylamines are easily accomplished since the amino group activates the aromatic ring. Thus, DPA reacts with bromine or chlorine to form the 2,2',4,4' tetrahalo derivative; nitration usually produces the trinitro compound.

Hydrogenation of diarylamines yields dialcyclic amines, but hydrogenolysis of the carbon-nitrogen bond also occurs. Dehydrogenation of DPA yields carbazole and alkyl derivatives of DPA give acridines. Dehydrogenation with sulfur gives phenothiazines (12).

Since diarylamines are relatively weak bases, they react relatively slowly, or not at all, in typical amine reactions. Diarylamines undergo Mannich reactions with a variety of active hydrogen compounds (13). Formaldehyde reacts with DPA to give *N,N,N',N'*-tetraphenylmethylenediamine [21905-92-0]. In the presence of strong acids, this rearranges to the ring-substituted product 4,4'-(dianilino)-diphenylmethane and higher polydiarylamines. Nitrous acid and other nitrosating agents easily give *N*-nitroso derivatives. These compounds can be rearranged to the ring-substituted DPA. Thus, *N*-nitrosodiphenylamine [86-30-6], with excess anhydrous HCl in alcohol, at low temperatures, gives 4-nitrosodiphenylamine [156-10-5] in excellent yields (14). Nitrosyl chloride and DPA, under the same conditions, lead directly to the 4-nitrosodiphenylamine. Water must be avoided in the reaction since it reacts with nitrosyl chloride.

Diarylamines do not react with carbon disulfide, whereas dialkylamines readily form dithiocarbamates. However, *N,N'*-diaryldithiocarbamates can be prepared from metal salts of diarylamines and carbon disulfide (15). They are more stable than dialkyldithiocarbamic acids, eg, *N,N'*-diphenyldithiocarbamic acid [7283-79-6], mp 142°C. Similarly, various metal salts of DPA react with carbon dioxide and an epoxide to give the β -hydroxyalkyldiphenylcarbamates (16).

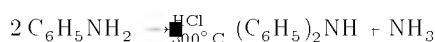
Diarylamines can be *N*-alkylated with anhydrides and acyl halides or *N*-alkylated with alkyl halides, alkyl sulfates, and tri-*n*-alkylphosphites.

Diphenylamine derivatives of alkyl-aryl gallium, germanium, phosphorus, and silicon are known (17), eg, pentaphenylgermanamine [64653-46-9].

Manufacture

Diarylamines are manufactured by the self-condensation of a primary aromatic amine in the presence of an acid, or the reaction of an arylamine with a phenol, at high temperatures.

Diphenylamine is manufactured by the self-condensation of aniline in the presence of a small amount of a mineral acid, such as anhydrous hydrogen chloride, or Lewis acids, such as ferrous chloride or ammonium bromide.



Thermodynamic analysis of this reaction shows favorable energy relations (18). The standard free energy of formation of DPA is 310.5 kJ/mol (74.2 kcal/mol) (19).

The reaction may be carried out in a corrosion-resistant apparatus fitted with an appropriate fractionating column. Here, the ammonia is separated from the aniline and removed from the reaction. The pressure is controlled to maintain the temperature near 300°C. When conversion reaches 50–60%, the

excess aniline is distilled and the pure diphenylamine is then isolated by vacuum distillation. Yields range from 83 to 95% (20,21).

The vapor-phase conversion of aniline to DPA over a solid catalyst has been extensively studied (18,22). In general, the catalyst used is pure aluminum oxide or titanium oxide, prepared under special conditions (18). Promoters, such as copper chromite, nickel chloride, phosphoric acid, and ammonium fluoride, have also been recommended. Reaction temperatures are usually from 400 to 500°C. Coke formed on the catalyst is removed occasionally by burning. In this way, conversions of about 35% and yields of 95% have been reported. Carbazole is frequently a by-product.

The second major route to diarylamines is the condensation of an aromatic amine with a phenol. Aniline [62-53-3], phenol [108-95-2], and 3.5% phosphoric acid at 325°C gives a 50% yield of DPA (23). Apparently, this reaction involves the addition of aniline to the keto form of the phenol. Thus, naphthols and hydroquinone are more reactive and give higher yields of product. This is the preferred route to *N*-phenyl-2-naphthylamine, 4-hydroxydiphenylamine, and *N,N'* diphenyl-*p*-phenylenediamine (24).

A process for the production of DPA from phenol and ammonia has been reported (25). Typically, the reaction is carried out continuously in a fixed-bed reactor using an acidic alumina catalyst at 300°C–420°C. The first product formed is aniline which is subsequently converted to DPA. Consequently, the reaction can be carried out to simultaneously produce DPA and aniline, in any desired ratio, simply by varying the molar ratios of phenol (and aniline) in the reactor feed stream.

Aromatic amines also react with halobenzenes to produce diarylamines. DPA forms when aniline and chlorobenzene are heated together. This reaction takes on commercial significance when the halobenzene is activated by an electron withdrawing group. The reaction of *p*-nitrochlorobenzene with aniline in the presence of copper cyanide and potassium carbonate at 200°C has been used to manufacture *p*-nitrodiphenylamine [836-30-6] (26). The preparation of *p*-nitrodiphenylamine has been improved by the reaction of the formamide of aniline with *p*-chloronitrobenzene in the presence of potassium carbonate at 165°C (27). The *p*-nitrodiphenylamine can be easily reduced to *p*-aminodiphenylamine, a precursor to several commercial *p*-phenylenediamine antiozonants (qv). These compounds can also be prepared by the self-condensation of nitrosobenzene to *p*-nitrosodiphenylhydroxylamine [28548-57-4] followed by reductive alkylation (28).

According to the U.S. International Trade Commission's Synthetic Organic Chemicals, Production and Sales, 1987, the three manufacturers of diphenylamine are Rubicon, Inc., Aristech Chemical Corp., and Uniroyal Chemical Co. No production figures have been given since 1974, but U.S. production in the range of 5,000–10,000 t yr appears reasonable.

Laboratory Procedures

Specific diarylamines not easily obtained by the above methods can be prepared by the Ullmann (29) and Chapman (30) reactions. For example, *m*-chloroaniline reacts with *o*-chlorobenzoic acid in the presence of potassium carbonate and a catalytic amount of a copper salt to give 2-[(3-chlorophenyl)amino]benzoic acid [13278-36-9], which is then decarboxylated on heating to 3-chlorodiphenylamine [101-17-7].

The Chapman synthesis makes use of an arylamine and a phenol. The arylamine is converted to the benzamide which then reacts with phosphorus pentachloride to give the *N*-aryl- α -chlorobenzylideneimine. Reaction with the sodium salt of a phenol gives the arylimino ether which rearranges to the benzamide on heating. Hydrolysis with alcoholic potassium hydroxide gives the diarylamine in 80% yield. Benzamides hindered in the 2,6-positions are resistant to hydrolysis and cannot be prepared in this way. Alternatively, benzamides have been prepared by reaction of *p*-bromophenol with anilides, which are then hydrolyzed to diarylamines (31).

An additional method utilizes the reaction of metallic salts of primary aromatic amines with aryl halides, apparently via a benzyne intermediate. Thus, the sodium salt of *p*-toluidine reacts with *p*-bromotoluene to give a mixture containing di-*p*-tolylamine [620-93-9], *m,p*-ditolylamine [62121-57-7], and aminoditolyls (32).

Catalytic dehydrogenation of dicyclohexylamine [101-83-7], *N*-cyclohexylaniline [1821-36-9], or *N*-cyclohexylideneaniline [10592-26-4] with Pt–Al₂O₃ at 375°C gives 40% carbazole [86-74-8] and 20% DPA (33). The catalytic dehydrogenation of imines derived from cyclohexanones and aromatic amines can also be used to prepare diarylamines (34). Certain unsaturated imines can be isomerized and aromatized to diarylamines. Thus, the imine of carvone and aniline C₁H₁₉N [68388-27-2] when treated with rhodium chloride in ethanol containing potassium carbonate at 100°C gives a 50% yield of 2-methyl-5-isopropylidiphenylamine [68388-29-4] (35).

Analysis

Diarylamines may be identified by melting point. Chromatographic techniques, such as hplc, gc, and tlc, are especially useful for separating and identifying diarylamines. Infrared, uv, nmr, x-ray and mass spectroscopy are also used. Diarylamines are also used as analytical reagents in the detection of various materials, eg, *N,N'*-[iminobis(9,10-dihydro-9,10-dioxo-4,1-anthracenediyl)]bis-benzamide [128-79-0] for boron, germanium, selenium, and tellurium and 2,2',4,4',6,6'-hexanitrodiphenylamine [131-73-7] has been used for potassium. As a spot test, diphenylamine in concentrated sulfuric acid with oxidizing agents produces a blue color.

Toxicity

Diphenylamine in the basic diet of rats at 0.5–1.5% inhibits growth and causes liver and kidney disorders (36). Industrial poisoning by diphenylamine has been encountered and appears clinically as bladder symptoms, tachycardia, hypertension, and skin problems (37). There is no federal standard for permissible exposure limits in air, but the American Conference of Government Industrial Hygienists (1983–84) has adopted a Time Weighted Average value of 10 mg m⁻³ and set a Short Term Exposure Limit of 20 mg m⁻³. The alkylated diphenylamines, used as antioxidants, have much higher molecular weights and are relatively nonvolatile.

N-Nitrosodiphenylamine can act as a nitrosating agent for other amines with all the consequences thereof (see *N*-NITROSAMINES).

As with the parent aromatic hydrocarbons, diarylamines based on polycyclic aromatic amines also tend to be more harmful. Thus, *N*-phenyl-2-naphthylamine [135-88-6] (PBNA) metabolizes in the body to produce small amounts of 2-naphthylamine, a known carcinogen (37). ACGIH has designated PBNA to be an "industrial substance suspect of carcinogenic potential for man."

Uses

Diarylamines are of the greatest industrial importance as stabilizers and antioxidants (qv) for polymers, stabilizers for explosives, polymerization inhibitors, and in dyes. Today, the use of these materials as antioxidants is essentially limited to derivatives of diphenylamine since *N*-phenyl-2-naphthylamine is no longer used.

Diarylamines function as rubber antioxidants by breaking the peroxidative chain reactions leading to rubber deterioration. Nearly all commercial synthetic rubbers (see ELASTOMERS, SYNTHETIC), including neoprene, butyl, styrene–butadiene, and the acrylonitrile–butadiene rubbers, can be protected with about 1–2% of an alkylated diphenylamine. DPA itself is not used as a rubber antioxidant. An objectionable feature of these antioxidants is that they cause discoloration and staining which limits their use to applications where this is not important.

The 9,9-dimethylacridan formed in the reaction between diphenylamine and acetone, besides functioning as an antioxidant, also improves the flex life of rubber vulcanizates since it forms a more stable nitroxyl radical than the alkylated diphenylamines.

N-Aryl-*p*-phenylenediamines can be considered to be 4-amino substituted diarylamines. However, phenylenediamines are significantly different than diarylamines. *p*-Phenylenediamines possess antiozonant activity, deactivate prooxidative metal ions, and improve flexing properties while diarylamines do not. Nevertheless, DPA is the starting material used for the production of *N*-alkyl-*N'*-aryl-*p*-phenylenediamine antiozonants (see AMINES, PHENYLENEDIAMINES).

Diphenylamine antioxidants are also widely used to stabilize roofing asphalts, lubricating greases, silicone enamels, polyamides, acetal resins, and

other hydrocarbons. They have been used as corrosion inhibitors in glycol heat-exchanger fluids (antifreezes) and as volatile corrosion inhibitors for steel (see CORROSION AND CORROSION INHIBITORS). They also stabilize sulfur trioxide.

In explosives, diphenylamine stabilizes cellulose nitrate by reacting with nitrogen oxides (see EXPLOSIVES AND PROPELLANTS). The products formed include *N*-nitrosodiphenylamine and mono and polynitro derivatives.

The addition of 2,2',4,4',6-pentanitro-6'-methyldiphenylamine [64653-47-0] to seawater precipitates potassium (38). Aromatic amines, especially aminotetrahydronaphthalenes and their *N*-aryl derivatives, are efficient flotation agents for quartz. The use of DPA for image formation in films has been patented (39,40). Diarylamines are used as intermediates (41) for azo, sulfur, oxidative base, triarylmethane, oxazine, nitro, and safranine dyes (see DYES AND DYE INTERMEDIATES).

Diphenylamine inhibits the development of scald disease during prolonged cold storage of apples and pears (42–45). It prolongs the fresh appearance of cut snapdragons (46), controls weather fleck in tobacco, inhibits algae formation, and shows growth inhibitory activity in potatoes (47).

Diphenylamine has shown activity against the body louse, chiggers, housefly, and, as the chloro derivative, against the red spider mite. Diarylamines have also been reported to have antiradiation activity (48).

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METHYLENEDIANILINE

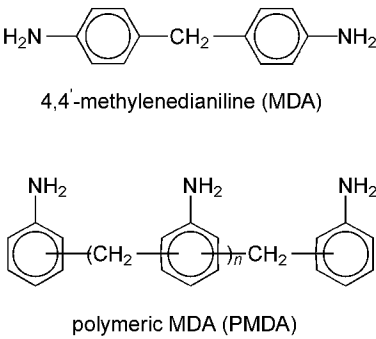
Commercial production of 4,4'-methylenedianiline [101-77-9] (4,4'-MDA) is carried out by the acid catalyzed reaction of formaldehyde with aniline. All processes produce polymeric MDA (PMDA), which consists of mixtures of isomers and oligomers of MDA . The amounts of MDA and oligomers are varied to produce products that have different applications. The isomeric distribution and the amount of MDA in the PMDA can be varied within wide ranges, depending on the needs of the consumer. More than 99% of the manufactured PMDA products are used in reactions with phosgene to produce the corresponding isocyanates for use in polyurethanes. The resultant polymeric isocyanates (PMDI) are either sold commercially or are purified to isolate 4,4'-methylenediphenyldiisocyanate (MDI) [101-68-8]. Only 15–20% of the total PMDI manufactured in the United States is consumed in the monomeric form. MDI is an important intermediate in the manufacture of spandex fibers, thermoplastic resins, and coatings, and it is used in reaction injection molding (RIM) for automotive applications. The primary use of PMDI products is in rigid foam insulation, but they are also used in semiflexible foams, foundry core binders, and particle board manufacture. Nonisocyanate uses for MDA or PMDA include epoxy curing agents, filament wound pipe, wire coatings, and military applications.

It is very difficult to treat MDA as a single entity because the manufacturing processes of PMDA and MDA are essentially identical, with the exception of a separation step. This article focuses on the technology of 4,4'-MDA, and it also includes properties of isomers and oligomeric mixtures when they are of commercial importance. The 4,4'-MDA is a suspected human carcinogen, and therefore special handling of this material is required. All of the MDA and PMDA produced is consumed in industries that are "destructive" of MDA's chemical identity. Thus MDA loses its unique chemical identity and is not encountered by household consumers.

The terminology commonly used to describe MDA and PMDA material is confusing to those new to the field. The term MDA is sometimes used for pure 4,4'-MDA as well as the oligomeric mixture PMDA. Similar inconsistencies are encountered for the isocyanate derivatives (MDI and PMDI). Synonyms for 4,4'-methylenedianiline include MDA, 4,4'-MDA, methylenedianiline, 4,4'-methylenebis(aniline), dianilinomethane, 4-(4'-aminobenzyl)aniline, 4,4'-diaminodiphenyl-methane, 4,4'-methylene-bis(benzenamine), bis(*p*-aminophenyl)methane, DADPM, DAPM, and DDM. The *p,p'*- and 4,4'-designations are used interchangeably. Synonyms for the oligomeric MDA mixtures include polyaminopolyphenylamine, polymethylenepolyphenylamine, and PMDA. In this article MDA will stand for 4,4'-MDA and or its isomers, and PMDA is a mixture of MDA and MDA oligomers.

Physical Properties

The physical and chemical properties of 4,4'-MDA and a typical PMDA are listed in Table 1.



Purified 4,4'-MDA is a light tan to white crystalline solid with a faint aminelike odor. It slowly oxidizes in air with a darkening in color. PMDA mixtures are yellow to brown supercooled liquids or waxy solids.

Table 1. Physical and Chemical Properties of MDA and PMDA

Property	4,4'-MDA	PMDA ^a
CAS Registry Number	[101-77-9]	[25214-70-4]
molecular formula	C ₁₅ H ₁₄ N ₂	
RTECS accession number ^b	BY5425000	
molecular weight	198.3	
active hydrogen equivalent weight	49.6	51
melting point, °C	93	60–80
heat of vaporization, kJ mol ^c	95.4	
specific heat, J (g° C)	2.1	2.1
heat of fusion, kJ mol ^c	19.6	~19.6
flash point, °C	227	238
boiling point, °C	238 at 1.33 kPa ^d	398 at 101.3 kPa ^d
vapor pressure, Pa ^d	2.7 × 10 ⁻⁵ at 25°C	1.3 at 100°C
density, g mL	1.070 at 103°C	1.07 at 70°C
viscosity, mPas(cP)	8.3 at 100°C	80 at 70°C
approximate solubility, g 100 mL solvent at 25°C		
acetone	273.0	
benzene	9.0	
carbon tetrachloride	0.7	
ethyl ether	9.5	
methanol	143.0	
water	0.1	

^a For PMDA containing approximately 70% MDA.

^b Registry of Toxic Effects of Chemical Substances.

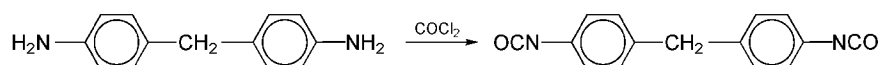
^c To convert kJ to kcal, divide by 4.184.

^d To convert kPa to mm Hg, multiply by 7.5.

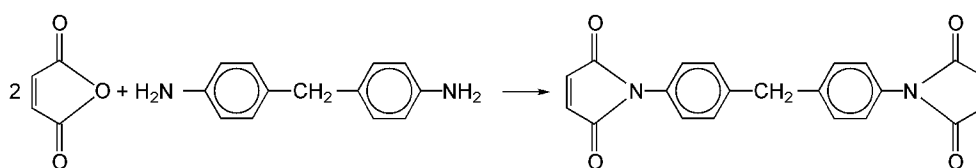
Chemical Properties

MDA reacts similarly to other aromatic amines under the proper conditions. For example, nitration, bromination, acetylation, and diazotization (1–3) all give the expected products. Much of the chemistry carried out on MDA takes advantage of the difunctionality of the molecule in reacting with multifunctional substrates to produce low and high molecular weight polymers.

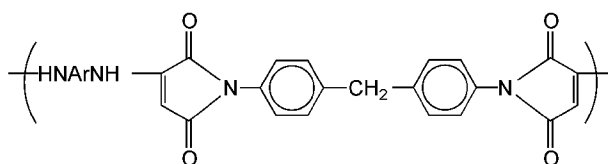
The most important commercial process is the reaction of MDA with an excess of phosgene to form the corresponding isocyanate, 4,4'-methylene-diphenyldiisocyanate, MDI, C₁₅H₁₀N₂O₂. The reaction proceeds through the formation of a primary carbamyl chloride that is decomposed with heating and the removal of HCl.



MDA reacts with acid anhydrides to form amides. In the reaction with maleic anhydride both of the amino hydrogens are replaced to form the imide, *N,N'*-(methylenedi-*p*-phenylene) dimaleimide [1367-54-5] C₂₁H₁₄N₂O₄.



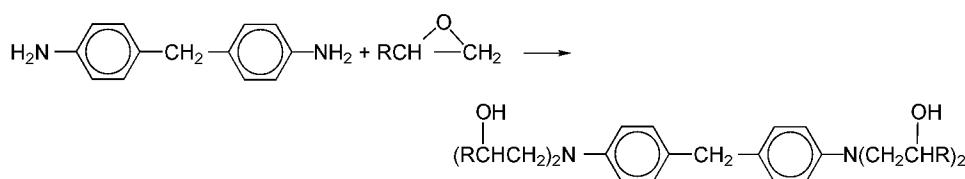
The bismaleimide can then be polymerized by reaction with additional amine to form polyaminobismaleimide or by radiation-induced homopolymerization to form polybismaleimide (4).



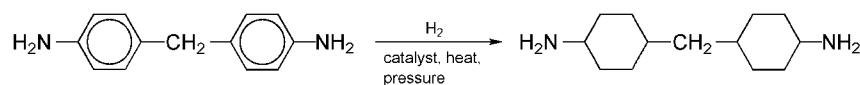
polyaminobismaleimide

The reaction of diphenic anhydride with excess MDA proceeds through an imide ring opening to produce a linear polymer, or it can react with PMDA to form a cross-linked polymer (5).

All of the amine hydrogens are replaced when MDA or PMDA reacts with epoxides to form amine based polyols. These polyols can be used in reactions with isocyanates to form urethanes or with additional epoxide to form cross-linked thermoset resins.



High temperature and high pressure reactions of MDA with hydrogen in the presence of noble metal catalysts convert 4,4'-MDA into bis(4-aminocyclohexyl)methane (H₁₂MDA) [1761-71-3] (C₁₃H₂ N₂). The products are a mixture of *cis* and *trans* isomers that can be controlled to some extent by the proper choice of catalyst and reaction conditions (6–12).



Manufacture and Processing

MDA and oligomers (PMDA) are produced by the acid catalyzed condensation of aniline [62-53-3] (C₇H₇N) with formaldehyde [50-00-0] (CH₂O). The reaction does not lead to a single product, but to a mixture of 4,4'-, 2,4'-, and 2,2'-isomers and oligomeric MDAs. The amounts of MDA isomers and oligomers formed depend on the ratios of aniline, formaldehyde, and acid used, as well as the reaction temperature and time. Figure 1 shows a simplified pathway to the formation of 4,4'-MDA. Similar routes can be drawn for the formation of 2,4'-MDA, 2,2'-MDA, and higher oligomers. The initial reaction of aniline with formaldehyde produces *N*-methylolamine [61224-32-6] (C₇H₉NO). This product loses water rapidly to form the Schiff base (intermediate A) (13,14). The Schiff base reacts with aniline to form two types of aminals, linear (LA) and cyclic (HHT). The relative amounts of the aminals formed depend on the ratio of aniline to formaldehyde. For example, when aniline: formaldehyde molar ratios of >2 : 1 are employed, the predominant product is the linear aminal with *n* = 1. If the reaction is carried out in base or in neutral solution, the reactions stop at this stage.

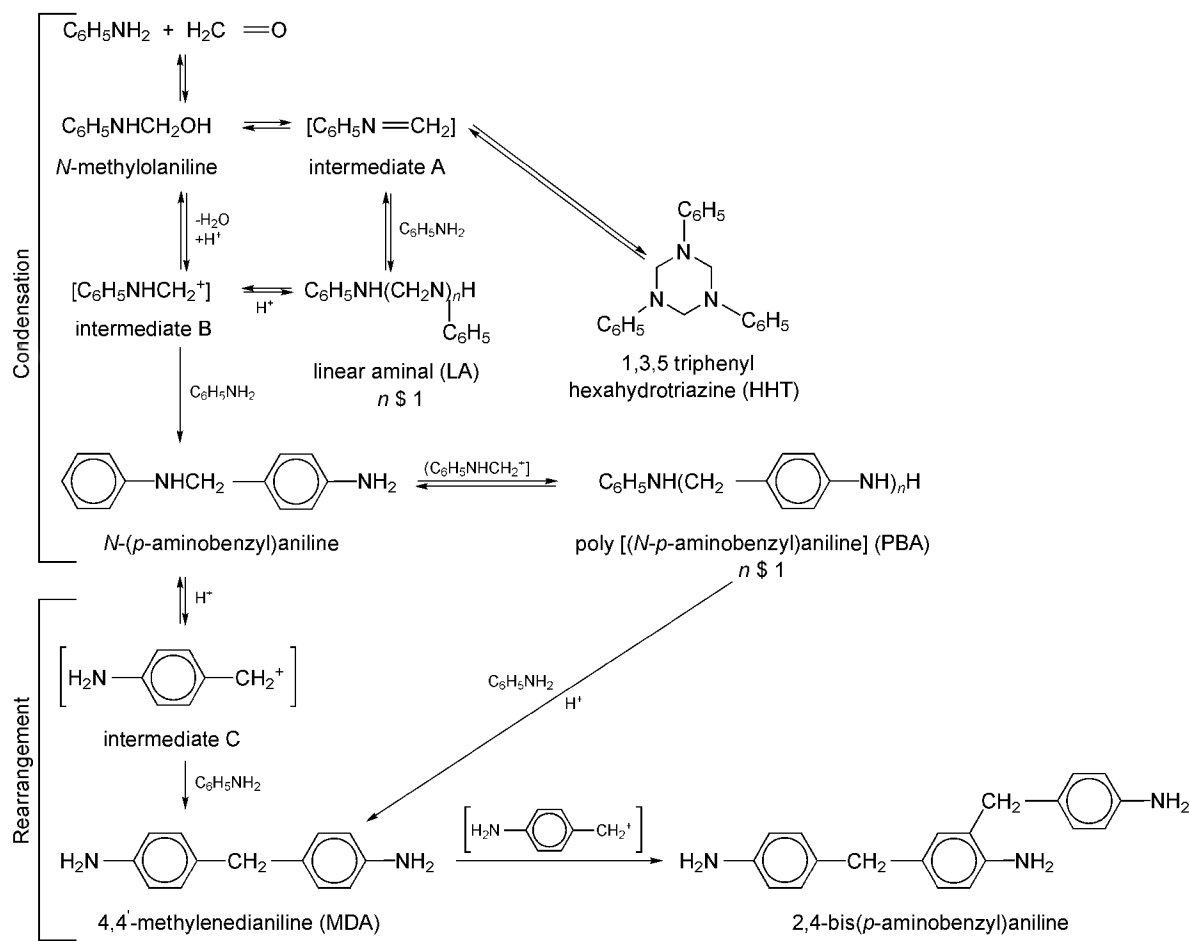


Fig. 1. Reaction of aniline with formaldehyde.

MDA does not form in the absence of acid. The aminals and the *N*-methylol aniline decompose rapidly in acid solution to form an anilinium ion (intermediate B). This reactive intermediate combines with aniline to form *N*-(*p*-aminobenzyl)aniline [17272-83-2] (C₁₃H₁₄N₂) which reacts with intermediate B in the presence of acid to form oligomeric benzylamines (PBA) that exist in equilibrium with the monomer. The formation of this equilibrium mixture completes the condensation phase of the synthesis. Almost all of the side reactions take place during the condensation phase of the reaction. The typical side products formed are the *N*-methyl and quinazoline derivatives of aniline and MDA (13,15). Commercial processes have been successful in minimizing these side reactions.

The final step (rearrangement stage of the reaction) is decomposition to form the *p*-aminobenzyl carbonium ion (intermediate C) and alkylation of aniline to form 4,4'-MDA. In this step all of the secondary amine intermediates are converted to primary amine final products. Direct alkylation of PBA with aniline has also been hypothesized to form MDA without the formation of intermediate C (16). The formation of MDA is not reversible under normal reaction conditions. Almost all of the other reactions depicted are reversible to some extent. From a commercial standpoint the most important reactions taking place are the formation of oligomers, ie, the reaction of MDA with intermediate C or PBA. It is these reactions, which cannot be suppressed, that are responsible for the current development of MDA technology. MDA is formed slowly during the reaction and therefore is susceptible to further alkylation to form 2,4-bis(*p*-aminobenzyl)aniline [25834-80-4] (C₂₀H₂₁N₃). Further alkylations produce an oligomeric mixture.

The reaction of aniline with formaldehyde can be carried out in a single reactor (Fig. 2). However, most commercial processes probably use multiple reactors, which provide greater control of the MDA isomer distribution and oligomeric content of the final product (17–20). Use of hydrochloric acid and high reaction temperatures necessitates the use of corrosion resistant metallurgy. Normally the acid is first mixed with excess aniline, which causes an exotherm. Formaldehyde is then added, with efficient agitation and at low temperatures (<50°C), to the aniline–aniline hydrochloride solution. The reaction is usually staged to control the condensation and rearrangement steps. The final reaction temperatures are normally 80–120°C. After completion of reaction, the acidic PMDA is treated with aqueous sodium hydroxide to neutralize the excess acid. A large amount of salt is formed during this step; thus the plants must be located near an outlet capable of handling the generated salt water (normally a seacoast). Processes that recycle the acid and eliminate the salt disposal problem have been patented (21,22). The organic layer is then washed with water and stripped to remove unreacted aniline and water. The unreacted aniline is recycled back to the beginning of the reaction. The product may be purified to isolate pure 4,4'-MDA, packaged for shipment, or treated with phosgene to produce the corresponding isocyanate. The 4,4'-MDA is normally sold in flaked or granular form in lined steel drums. Depending on the MDA content, PMDA is sold as a waxy solid or a yellow to brown viscous supercooled liquid in steel drums.

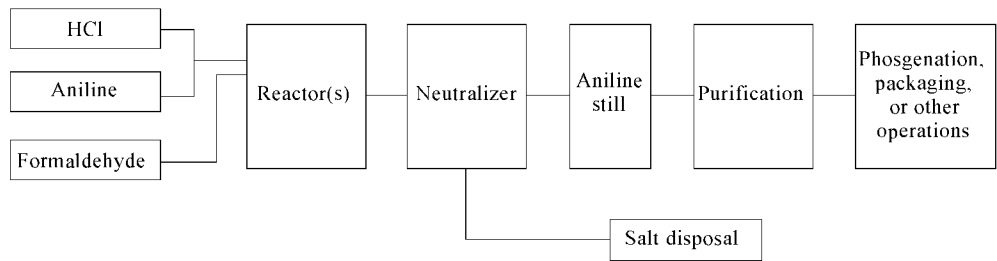


Fig. 2. Methylenedianiline process.

Process parameters can be varied to change the MDA isomer distribution and oligomeric content of PMDA products. Generally, aniline to formaldehyde molar ratios of 2 to 5 are used. To increase the MDA content, higher ratios of aniline to formaldehyde are employed. Increasing the acid to aniline ratio also increases the 4,4'-MDA content of the diamine fraction. Historically, the polyurethane industry consumes as much of the 4,4'-MDI isomer as possible. Recently, however, there has been an increasing demand for higher 2,4'-MDI and 2,4'-PMDI products to be used as replacements for

toluenediisocyanate (TDI). Low acid and high aniline to formaldehyde ratios increase the 2,4'-MDA content of the diamine fraction. At the lower aniline to formaldehyde ratios the tendency is to form higher oligomers. The 2,4'-MDA is more reactive toward alkylation than the 4,4'-MDA isomer. Commercial processes do not employ molar excesses of acid to aniline. Acid catalysis is necessary to form MDA, and HCl is the acid of choice. Silica (23), clay (24–26), ethanesulfonic acid (27), and tungsten (28,29) are among the catalysts that have been patented. All of these processes possess some commercial drawbacks, eg, high expense, severe reaction conditions, and or poor yields of 4,4'-MDA. High reaction temperatures result in a decrease in the MDA content of the product. Reaction time and water content also affect the oligomeric distribution of the product; both should be minimized for maximum MDA formation (30). Water is introduced into the reaction from the hydrochloric acid used to make the aniline hydrochloride solution, from the formaldehyde, which is normally sold in water solution (formalin), and as a reaction product in the condensation phase of the reaction.

Commercially, the PMDA mixtures are normally treated with phosgene to produce the corresponding isocyanates. These isocyanate mixtures, commonly called polymeric MDI (PMDI), are sold directly and have varied chemical compositions. The 4,4'-MDI can be separated from the PMDI products by distillation or crystallization (31,32). The amount of 4,4'-MDI that is removed depends on marketing conditions. The residues are also viable commercial products.

Commercially, a small amount of the 4,4'-MDA is isolated by distillation from PMDA. Depending on the process employed, the removal of MDA can be partial (as is done with the isocyanates) or total. Partial removal of MDA gives some processing latitude but yields of 4,4'-MDA are reduced. Distillation residues from PMDA manufacture that contain less than 1% MDA pose a disposal problem. Processes for the regeneration of MDA by heating these residues in the presence of aniline and an acid catalyst have been patented (33–35). Waste disposal of PMDA is expensive and reclamation processes could become commercially viable. The versatility of the isocyanate process, however, can be used to avoid the formation of low MDA content distillation residues.

Economic Aspects

The data in Table 2 represent the total MDI (MDI and PMDI) that is produced on a global basis.

Table 2. 1989 Global Production Capacity for MDI and Polymeric MDI

Manufacturer	Location	Capacity ^a , 10 ³ t
United States ^b		
BASF	Geismar, La.	68
Dow	La Porte, Tex.	150
Mobay	Baytown, Tex.	100
	New Martinsville, W. Va.	50
Rubicon	Geismar, La.	141
Total United States		509
Western Europe ^c		
BASF	Antwerp, Belgium	60
Bayer	Krefeld, FRG	126
Bayer	Leverkusen, FRG	20
Bayer	Tarragona, Spain	6
Bayer-Shell	Antwerp, Belgium	26
ICI	Fleetwood, UK	45
ICI	Rosenberg, Holland	40
Montedison	Brindisi, Italy	70
Dow	Isopor, Portugal	50
Dow	Delfzijl, Holland	70
Total Western Europe		513
Asia ^d		
Dow-MDK	Yokkaichi, Japan	36
Mitsui Toatsu	Omuta, Japan	35
Nippon Polyurethane	Nanyo, Japan	50
Sumitomo Bayer	Niihama, Japan	36
Total Asia		157
other (Eastern Europe and South America)		ca 61
Global total		1,240

^a The conversion factor for PMDA to PMDI is 1.25–1.35; eg, 80 kg of MDA produces 100 kg of MDI.

^b Ref. 36.

^c Ref. 37.

^d Ref. 38.

The estimated growth rate to the year 2000 for total MDI is 4–5% in the United States and 6% globally. In 1987 and 1988 U.S. plants were estimated to be 96 and 97% utilized (39). Additional capacities of over 400,000 t by the end of 1993 have already been announced (40–44). Approximately 20% of the total MDI manufactured in the United States is exported (38,39,45). Of the 500,000 t of PMDI mixtures manufactured annually in the United States it is estimated that only 75,000–100,000 t are sold as 4,4'-MDI. The current bulk selling price for 4,4'-MDI is \$2.75/kg and for PMDI \$2.20. The 4,4'-MDA sells for \$5.00–6.50/kg and crude PMDA is \$2.90–3.25/kg. Approximately 450–900 t of pure 4,4'-MDA are imported (46,47), MDA and PMDA products are sold commercially under the names of MDA (BASF), Araldite Hardener (CIBA-GEIGY), Curithane (Dow), Ancamine (Pacific Anchor), and TONOX (Uniroyal).

Specifications and Standards

The 4,4'-MDA is sold commercially with a diamine assay of 98–99%. The major impurity is the 2,4'-MDA isomer, which can be present in amounts up to 3%. PMDA products are normally defined by hydrogen equivalent weight and viscosity. Typical products exhibit a 50 hydrogen equivalent weight and a viscosity of 80–140 mPas (cP) at 70°C. PMDA products normally contain, in addition to the isomers and oligomers of MDA, small amounts of aniline, water, chlorides, and various alkylated amines. All MDA products should be stored in sealed containers in a cool dry area.

Analytical and Test Methods

The characterizations of MDA and PMDA are similar to those normally used for aromatic amines. In the manufacture of PMDA, the MDA isomer distribution and the formation of side products is determined primarily by gas chromatography (48,49). The amine content is determined by acid titration

or diazotization. PMDA oligomeric distributions are determined by hplc or gpc techniques (49) and are estimated by viscosity measurements. Liquid chromatographic and spectrophotometric monitoring methods have been developed to determine ppm to low ppb quantities in workplace environments (50,51), urine (52), reacted polyurethanes (53), and epoxy systems (54). All of the environmental methods of analysis employ a collection technique that is sensitive to the presence of aerosols and are capable of quantitating MDA down to 10 ppb (v v). OSHA recommends using Method #57 for monitoring purposes (55).

Health and Safety Factors (Toxicology)

All of the toxicity data on MDA have been collected using either 4,4'-MDA or the corresponding hydrochloride salt. The information discussed in this section can also be used for commercial products containing MDA or PMDA. Because MDA is a potentially hazardous chemical, worker exposure should be kept to a minimum. For complete health and safety information on MDA consult references 46 and 56–59.

The recommended threshold limit value (TLV) of MDA is 100 ppb for an 8-h time-weighted average (TWA) skin. MDA is a suspected human carcinogen (56,58,59). The oral LD₅₀ 830 mg kg. In May of 1989 OSHA proposed a new standard for regulating MDA. The proposal cites a permissible exposure limit (PEL) for occupational exposure of MDA to an 8-h TWA of 10 ppb and a STEL (short-term exposure limit) of 100 ppb for a 15-min TWA (50). The standard does not apply if initial monitoring shows less than the action level of 5 ppb for an 8-h TWA (airborne) and if no dermal exposure is likely. The employer is required to implement engineering and work practices (eg, respirators) to maintain employee exposure levels at less than or equal to the permissible exposure limit. The proposal also includes having a changing room and showers for changing all contaminated clothing after a work shift; employer laundering of clothing; removal of clothing prior to eating, drinking, smoking, etc; and washing hands and face prior to eating. If food and beverages are consumed in the work area, the employer is expected to provide a positive pressure eating area. All surfaces must be maintained as free as possible from visible accumulations of MDA. The employer is responsible for conducting medical surveillance and record keeping, as well as for conducting periodic monitoring of the area according to existing exposure level guidelines.

The major exposure route in workers who experience MDA poisoning is by skin contact. If there is a likelihood of skin or eye contact, proper protective clothing (including gloves, head coverings, impervious shoes, aprons, coveralls, or other full body clothing) must be worn. Skin absorption is increased if the MDA is dissolved in an organic solvent. Face shields and or goggles should be worn where appropriate. Care must be taken to minimize contamination of individuals and their personal environment from exposure to MDA. The low vapor pressure of MDA poses a minimum risk of MDA inhalation. However, grinding and drumming of MDA produces dust and vapors, which can cause inhalation problems. In addition, many operations require heating MDA to keep the material molten. It is therefore recommended that respirators be worn while handling MDA to keep exposures to a minimum.

There are no reports of cancer in humans as a result of MDA exposure. Acute exposures of MDA have caused epigastric pain, fever, jaundice, and other symptoms consistent with hepatitis. These effects, however, appear to be reversible. No liver damage has yet been observed from chronic exposure to MDA. Skin sensitivity and staining occurs in some individuals. In animals, chronic administration of MDA produces hepatic cirrhosis, liver lesions, and enlargement of the spleen, liver, and kidneys. MDA has also proved to be carcinogenic in rats and mice, causing liver and thyroid tumors. No cancers have been formed in dogs. Structurally similar compounds have been shown to cause cancer in laboratory animals (58). If appreciable amounts of MDA are swallowed, vomiting should be induced. If eye exposure does occur, the eyes should be flushed with water for 30 min. Skin exposures should be washed with soap and water. Medical attention should be obtained promptly whenever an exposure occurs. There are always dangers involved with the misuse of any chemical. However, with attention to proper work practices and policies, this valuable intermediate can be utilized safely.

Uses

More than 99% of all the PMDA produced is used directly in the manufacture of the corresponding isocyanates (MDI and PMDI). Two types of isocyanates are sold, monomeric (MDI) and polymeric (PMDI). The PMDI products are available commercially in varying viscosities from 50 to 2000 mPas(cP), containing from 25 to 60% monomeric MDI. The major use for PMDI products (65–75%) is in the manufacture of rigid foam, which is primarily used in housing and refrigeration insulation applications. Other uses for PMDI products include semiflexible foam , elastomers, foundry core binders, and particle board adhesives. MDI contains approximately 98% of the 4,4'-isomer and is used to manufacture thermoplastic resins (eg, films, gaskets, tubing), spandex fibers, and coatings. Because MDI is a solid at room temperature, a significant portion of the commercially produced pure MDI is converted to liquid products by either modifying the MDI with carbodiimide linkages or reaction with polyols to produce isocyanate terminated prepolymers. These products are used in automotive reaction injection molding (RIM), coatings, and recreation and military applications. MDI and PMDI products containing more than 10% of the 2,4'-MDI isomer are becoming available for use in nonrigid foam applications. These products are able to compete with toluenediisocyanate (TDI) in physical properties of the final products without the severe handling limitations normally needed for TDI. Nonisocyanate uses for MDA or PMDA include epoxy resin curing agents, wire coating applications, plastic fibers, polyurethane coreactants, an intermediate for pigments and dyes, intermediates for the preparation of polyamide –imide resins, reinforced composite materials, and military applications. Perhydrogenated 4,4'-MDA (H₁₂MDA or PACM) is used in light-stable elastomers and coatings. The H₁₂MDA is converted to the corresponding isocyanate, bis(4-isocyanatocyclohexyl)methane [5124-30-1] (C₁₅H₂₂N₂O₂) or H₁₂MDI, and is used in automotive safety glass and biomedical applications.

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PHENYLENEDIAMINES

Phenylenediamines are aromatic amines with two amino groups attached to benzene. They are called benzenediamines by *Chemical Abstracts*. There are three phenylenediamines; ortho, meta, and para; or 1,2-; 1,3-; and 1,4-benzenediamines, respectively. Since they are difunctional, they are easily converted to polymers. The *m*-phenylenediamines are the least expensive isomers and are used in the largest volumes for the manufacture of polyurethanes (see URETHANE POLYMERS). *p*-Phenylenediamine is used for the manufacture of polyamides with exceptional tensile strength (see HIGH PERFORMANCE FIBERS; POLYAMIDES; and POLYIMIDES). The use of *o*-phenylenediamines for polymer formation is limited, but polybenzimidazoles and polyquinoxalines have been made (see HEAT RESISTANT POLYMERS). However, it is the unique chemistry of the *p*-phenylenediamine derivatives that makes them useful in the photographic and dye industries, and widely used as antioxidants (qv) and antiozonants (qv) for rubbers and plastics (see AZINE DYES; AZO DYES; COLOR PHOTOGRAPHY; COSMETICS; HAIR PREPARATIONS; and SULFUR DYES).

Physical Properties

The three phenylenediamines are all white solids when pure, but darken after standing in air. They are all very soluble in hot water, for example, about 700 g of *o*- or *p*-phenylenediamine are soluble in 100 ml. of water at 100°C whereas at room temperature only 4 g dissolve. The physical properties of the phenylenediamines and some of their more important derivatives are given in Table 1. Certain imines of *p*-phenylenediamine are liquid crystals (1). For example, N,N'-bis[*p*-(octadecyloxy)benzylidene]-*p*-phenylenediamine [24679-0508] has a mp of 129, 147, and 183°C (see LIQUID CRYSTALLINE MATERIALS).

Table 1. Physical Properties of Phenylenediamines

Phenylenediamine	Molecular formula	CAS Registry Number	Appearance	MP, °C	BP ^a , °C	Synthetic route	Price \$ kg
orthophenylenediamine ^b	C ₆ H ₈ N ₂	[95-54-5]	white solid	102	256–258 (dec)	ammonol, reduction of <i>o</i> -chloronitrobenzene	7.16
metaphenylenediamine ^b	C ₆ H ₈ N ₂	[108-45-2]	white solid	63	287	catalytic reduction of <i>m</i> -dinitrobenzene	4.56
paraphenylenediamine ^b	C ₆ H ₈ N ₂	[106-50-3]	white solid	140	267	ammonol, reduction of <i>p</i> -chloronitrobenzene	8.82
toluene-2,4-diamine	C ₇ H ₁₀ N ₂	[95-80-7]		99	280	reduction of 2,4-dinitro-toluene	
toluene-2,6-diamine	C ₇ H ₁₀ N ₂	[823-40-5]		105		reduction of 2,6-dinitro-toluene	2.82 ^c
2,3,5,6-tetramethyl- <i>p</i> -phenylene diamine	C ₁₀ H ₁₄ N ₂	[3102-87-2]	tan colored	151–152		nitration, reduction of durene	
<i>N,N</i> -dimethyl- <i>p</i> -phenyl-enedia mine	C ₈ H ₁₂ N ₂	[99-98-9]		41	262	nitrosation, reduction of <i>N,N</i> -dimethylaniline	
<i>N,N</i> -diethyl- <i>p</i> -phenyl-enediame ne	C ₁₀ H ₁₄ N ₂	[93-05-0]	pale yellow oil		260–262	reduction of <i>p</i> -nitro- <i>N,N</i> -diethylaniline	
<i>N,N'</i> -bis(1-methylpropyl)- <i>p</i> -ph enylenediamine	C ₁₄ H ₂₄ N ₂	[101-96-2]	pale yellow oil		98 (26.6 Pa ^d)	reductive alkylation of <i>p</i> -phenylenediamine	
<i>N,N'</i> -bis(1-methylheptyl)- <i>p</i> -ph enylenediamine	C ₂₂ H ₄₀ N ₂	[103-96-8]	low melting white solid		190 (40 Pa ^d)	reductive alkylation of <i>p</i> -phenylenediamine	6.81
<i>N,N'</i> -bis(1-methylpropyl)- <i>N,N'</i> -dimethyl- <i>p</i> -phenyl-enedia mine	C ₁₄ H ₂₈ N ₂	[87-98-9]	oil		115 (20 Pa ^d)	Leuckart-Wallach reaction	
<i>N</i> -phenyl- <i>p</i> -phenylenediamine	C ₁₂ H ₁₂ N ₂	[101-54-2]		75	354	nitrosation, reduction of diphenylamine	
<i>N,N'</i> -diphenyl- <i>p</i> -phenyl-enedia mine	C ₁₈ H ₁₄ N ₂	[74-31-7]	white solid	146		from hydroquinone and aniline, acid cat	10.38
<i>N,N'</i> -di-2-naphthalenyl- <i>p</i> -phen ylenediamine	C ₂₂ H ₂₀ N ₂	[93-46-9]		236		from 2-naphthol and <i>p</i> -phenylenediamine, heat	13.78
<i>N</i> -1-methylethyl- <i>N'</i> -phenyl- <i>p</i> -p henylenediamine	C ₁₅ H ₁₈ N ₂	[101-72-4]		78		reductive alkylation of <i>N</i> -phenyl- <i>p</i> -phenylene-dia mine	7.61
<i>N</i> -(1,3-dimethylbutyl)- <i>N'</i> -phen yl- <i>p</i> -phenyl-enedia mine	C ₁₈ H ₂₄ N ₂	[793-24-8]		48–50		reductive alkylation of <i>p</i> -aminodiphenylamine with methyl isobutyl ketone	7.14
<i>N</i> -cyclohexyl- <i>N'</i> -phenyl- <i>p</i> -phe nylenediamine	C ₁₈ H ₂₂ N ₂	[101-87-1]				reductive alkylation of <i>p</i> -aminodiphenylamine with cyclohexanone	7.54

^a At 101.3 kPa = 1 atm unless otherwise noted.
^b The *K*_s of *o*-, *m*-, and *p*-phenylenediamine are 3.2 × 10⁻¹⁰, 7.6 × 10⁻¹⁰, and 1.1 × 10⁻⁸, respectively.
^c Price of the mixed diisocyanate.
^d To convert Pa to mm Hg, multiply by 0.0075.

Chemical Properties

The phenylenediamines are aromatic amines which undergo typical amine reactions, such as *N*-acylation and *N*-alkylation. However, unlike most aromatic amines, they cannot easily be alkylated on the aromatic ring using an olefin and an acid catalyst since protonation of the second amino group deactivates the ring. Consequently, most of the chemistry of the phenylenediamines involves reactions on the nitrogen. Commercially the largest volume usage of phenylenediamines is in the manufacture of diisocyanates; large volumes of *N,N'*-alkyl aryl-*p*-phenylenediamines are also manufactured.

o-Phenylenediamines favor the formation of five- and six-membered rings and undergo many reactions which involve cyclization to give heterocyclic compounds. Anhydrides, acids, amides, and esters give benzimidazoles (2); cyanogen chloride gives the 2-aminobenzothiazole (3); 1,2-dicarbonyl compounds (4) and propargyl alcohols (5) give quinoxalines; methyl ketones give 1,5-benzodiazepines (6); *o*-chlorobenzoic acids (7) and chromones and flavones give benzodiazepinediones (8); β-ketoesters give benzodiazepinones (9); nitrous acid gives triazoles; and phosphorus and boron compounds (10) give five-membered ring heterocyclic compounds. Large ring annulenes can also be prepared from certain α,β-unsaturated aldehydes (11).

The *p*-phenylenediamines are special and are used in many applications where the other isomers are ineffective. They are unique because they are more readily oxidized than the meta or ortho isomers, as seen by the ionization potentials listed in Table 2. The enhanced reactivity of *p*-phenylenediamine is due to the high degree of resonance stabilization of its radical cation.



Table 2. Ionization Potentials of Phenylenediamines

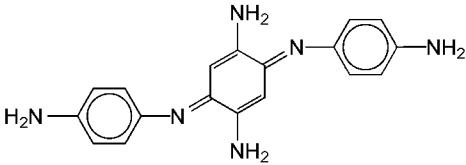
Compound	CAS Registry Number	Ionization potential, eV
<i>N,N,N',N'</i> -tetramethyl- <i>p</i> -phenylenediamine	[100-22-1]	5.97
<i>N,N</i> -diethyl- <i>p</i> -phenylenediamine	[93-05-0]	6.04
<i>p</i> -phenylenediamine	[106-50-3]	6.52
<i>m</i> -phenylenediamine	[108-45-2]	7.26
<i>o</i> -phenylenediamine	[95-54-5]	7.29
aniline	[62-53-3]	7.70

Most oxy or halo free radicals readily oxidize *p*-phenylenediamines to radical cations called Wurster salts (12), which are stable in water-ethanol solutions at pH 3. On the other hand, carbon and sulfur radicals generally do not produce Wurster salts. The intense color of Wurster salts can be used as a quick spot test for variously substituted *p*-phenylenediamines when oxidized with bromine in carbon tetrachloride solution. For example, *N,N'*-dialkyl substitution gives red, *N,N,N',N'* gives blue, and *N*-alkyl-*N'*-aryl gives light blue or green.

Because of their ease of oxidation, *p*-phenylenediamines are used as antioxidants, antiozonants, dye intermediates, and reducing agents in color photography. This is clearly seen with *N,N,N',N'*-tetramethyl-*p*-phenylenediamine, which has no labile hydrogen atom, yet still functions as an antioxidant by reducing peroxy radicals into anions. The facile one-electron oxidation of *N,N*-dialkyl-*p*-phenylenediamine makes it an important developing agent of light-sensitized silver salts in color photography (13). Similarly, oxidation of a mixture of 2,5-toluenediamine [95-70-5], aniline, and *o*-toluidine gives a red azine dye, Safranine T: oxazines and thiazines are made in an analogous way (14). Azomethine dyes are obtained when a *p*-phenylenediamine is oxidized in the presence of compounds containing active hydrogens (15).

Among aromatic amines, only *p*-phenylenediamines exhibit antiozonant activity because they react faster than other aromatic amines with ozone (see ANTIOZONANTS). Undoubtedly, this is due to their low ionization potential and their ability to react free-radically with ozone. Besides scavenging the ozone, *p*-phenylenediamines react with ozone to form high molecular weight products which act as physical barriers to ozone and retard further attack. The chemistry of this process involves reactions at three sites: (1) The side chain is oxidized to yield amides, nitro, and nitroso compounds, (2) the phenylenediamine ring is oxidized to quinonediimines (and their oxides) which add free amine to produce high molecular weight Bandrowski bases, (3) dimerization through the nitrogens give hydrazines (16). All of the above products can form from the first reaction product of ozone with the *p*-phenylenediamine, the Wurster salt.

An important mode of oxidation for *p*-phenylenediamines is the formation of *p*-benzoquinonediimines, easily obtained by oxidation with silver oxide in ether solution (17). Diimines undergo 1,4 additions with amines to generate tri- and tetraamines which readily oxidize in air to highly conjugated, colored products. An example of this is the formation of Bandrowski’s base [20048-27-5] when *p*-phenylenediamine is oxidized with potassium ferricyanide (18).



Bandrowski’s base

Most diimines are unstable and polymerize with great ease. They also readily hydrolyze to amines and quinones. Thus *p*-phenylenediamine can be oxidized directly to *p*-benzoquinone with manganese dioxide in aqueous sulfuric acid. Alkyl substitution increases stability only slightly whereas the *N*-aryl or *N,N'*-diaryl derivatives are stable. *N,N'*-Diphenyl-*p*-benzoquinonediimine [6246-98-6] is an orange solid, mp 187°C, prepared by heating *N,N'*-dinitroso-*N,N'*-diphenyl-*p*-phenylenediamine [2716-09-8] at about 100°C. *N,N'*-Dibenzene-sulfonyl-*p*-benzoquinonediimine [1050-82-4], mp 179°C, readily undergoes Diels-Alder addition reactions with dienes, whereas the *N*-aryl diimines react sluggishly (19). *o*-Phenylenediamine is also oxidized to *o*-benzoquinonediimine [4377-73-5] by silver oxide in ether.

Both the *m*- and *p*-phenylenediamines are used to manufacture sulfur dyes, either by refluxing in aqueous sodium polysulfide, or heating with elementary sulfur at 330°C to give the leuco form of the dye. These dyes are polymeric, high molecular weight compounds, and soluble in base. The color is developed by oxidation on the fabric. 2,4-Toluenediamine and sulfur give Sulfur Orange 1 (14).

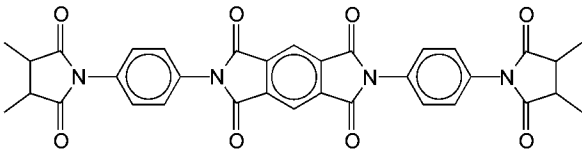
p-Phenylenediamines can be diazotized and tetrazotized (20), giving intermediates for various azo dyes (qv). Their diazonium salts are commercially manufactured and used in photography.

Polymerization

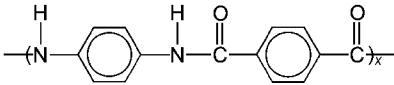
Until the mid-1960s, phenylenediamines were used primarily for oxidative purposes; the para isomer was of major importance. Since then, the use of phenylenediamines to manufacture polymers has far exceeded their use for oxidative purposes. The *m*-phenylenediamines, (2,4 and 2,6)-toluenediamine, are widely used for the manufacture of polyurethanes. Phenylenediamines are difunctional and react with other difunctional compounds, such as dianhydrides, diacyl chlorides, dicarboxylic acids, and disulfonyl chlorides to give polyamides . Phenylenediamines also give polymers with epoxides, diols, diacetals,

diisocyanates, diesters, etc. These aromatic polymers are being investigated for high temperature applications (see HEAT RESISTANT POLYMERS), and for use as electric conductors (21) (see ELECTRICALLY CONDUCTIVE POLYMERS).

p-Phenylenediamine is used to make heat-resistant polyimides by reaction with pyromellitic anhydride (see POLYIMIDES).

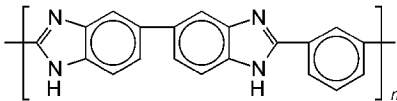


Both *m*- and *p*-phenylenediamine react with benzenedicarbonyl dichlorides to give linear, fully aromatic polyamides (see HIGH PERFORMANCE FIBERS).



Polymers from the meta isomer are useful for their heat and flame resistance; polymers from the para isomer are noted for high tensile strength and high modulus.

o-Phenylenediamines react with most functional groups to give cyclic compounds. Therefore bis-*o*-phenylenediamines, ie, tetraamines, are required for polymer formation. For example, polybenzimidazoles are obtained from 4,4'-oxybis-(1,2-benzenediamine) [26776-59-7], or 4,4'-sulfonylbis-(1,2-benzenediamine) [13224-79-8], and dicarboxylic acids.



Polyquinoxalines can be obtained in a similar fashion using bis-1,2-diketones (see HEAT RESISTANT POLYMERS).

Production

The *m*-phenylenediamines are easily obtained by dinitrating, followed by catalytically hydrogenating, an aromatic hydrocarbon. Thus, the toluenediamines are manufactured by nitrating toluene with a mixture of sulfuric acid, nitric acid, and 23% water at 330°C which first produces a mixture (60:40) of the ortho and para mononitrotoluenes. Further nitration produces the 80:20 mixture of 2,4- and 2,6-dinitrotoluene. Catalytic hydrogenation produces the commercial mixture of diamines which, when converted to diisocyanates, are widely used in the production of polyurethanes (see AMINES, AROMATIC, DIAMINOTOLUENES) (22).

The ortho and para isomers are obtained by catalytically hydrogenating the corresponding nitroanilines, made by heating the chloronitrobenzene with aqueous ammonia at about 450°C under pressure. These isomers can also be prepared by heating the corresponding dichlorobenzenes with aqueous ammonia at 210°C under pressure in the presence of a copper salt (23).

N-Phenyl-*p*-phenylenediamine [101-54-2], can be manufactured by heating aniline with *p*-chloronitrobenzene in the presence of a copper salt and catalytically hydrogenating the nitro group (24,25). The preparation of *p*-nitrodiphenylamine has been improved by the reaction of the formamide of aniline with *p*-chloronitrobenzene in the presence of potassium carbonate at 165°C (26). Alternatively, diphenylamine can be *N*-nitrosated and then rearranged to 4-nitrosodiphenylamine [156-10-5] with anhydrous hydrogen chloride (27) followed by reduction. Commercial antiozonants are prepared by reductively alkylating this diamine. A novel route to these antiozonants is the acid catalyzed self-condensation of nitrosobenzene to give *p*-nitroso-diphenylhydroxylamine [28548-57-4] followed by reductive alkylation (28).

The *N,N'*-diphenyl-*p*-phenylenediamine is prepared by heating hydroquinone with aniline in the presence of phosphoric acid (29). *N,N'*-di-2-naphthalenyl-*p*-phenylenediamine is made from *p*-phenylenediamine and 2-naphthol.

United States production of phenylenediamines is shown in Table 3 (30). Production of both the *m*- and *p*-phenylenediamines are not reported since they are produced captively for use in the manufacture of polyamides. However, aromatic polyamide plant capacity is about 30,000 t yr.

Table 3. United States Production of Phenylenediamine Derivatives, t^a

Year	2,4- and 2,6-Toluene diisocyanate (80 20)	N-Substituted <i>p</i> -phenylenediamines
1987	323,416	35,760
1986	301,589	32,680
1984	300,858	26,283
1982	252,195	24,057
1980	266,509	24,716
1975	282,138 ^b	33,550
1971	85,274 ^b	25,816
1967	40,160 ^b	21,641

^a United States International Trade Commission, Synthetic Organic Chemicals.

^b Calculated from reported toluenediamine production volumes.

Health and Safety

Like aniline, phenylenediamines may be toxic. *p*-Phenylenediamine causes irritation to the pharynx and larynx, and bronchial asthma, but dermatitis is the most common toxic effect. Appropriate substitution of *p*-phenylenediamine, generally on the nitrogen with phenyl or larger alkyl groups, significantly reduces its toxicity. Thus most commercial antioxidants and antiozonants show minimal skin sensitizing effects (31). The American Conference of Government Industrial Hygienists (1983 84) has set a TWA exposure limit at 0.1 mg m⁻³ and an "immediately dangerous to health" level of 25 mg m⁻³ (32). Correlation between structure and carcinogenicity of 23 phenylenediamines has been reviewed (33) and the toxicity test results of 22 compounds have been tabulated (34).

Uses

The largest volumes of phenylenediamines are used for the production of polymers, primarily polyurethanes, where the diisocyanates of toluenediamines (meta isomer) are used. For the manufacture of polyamides both meta and para isomers are used. Another significant use for *p*-phenylenediamines is as antioxidants and antiozonants for elastomers, plastics, and petroleum products. The *N*-alkyl-*N'*-aryl-*p*-phenylenediamines are by far the most commonly used and represent the bulk of the volume of the *N*-substituted *p*-phenylenediamines reported in Table 3. Some *N,N'*-dialkyl compounds are also still used as antiozonants, but they oxidize more rapidly and lose activity sooner. The *N,N'*-diaryl-*p*-phenylenediamines are used primarily as antioxidants, especially where copper and other harmful metals might be present. *N,N'*-Dinaphthalenyl-*p*-phenylenediamine is especially effective in this application. The *N,N'*-diphenyl compound has also been used as an anti-ozonant for neoprene rubber. The excellent reducing capability of these para diamines accounts for their use in these applications. For the same reason, they are also used in color photography and their diazonium salts are also used as photographic chemicals. The oxidation of *p*-phenylenediamines in the presence of amines and phenols is used to manufacture dyes. Many permanent hair dyes are based on the oxidation of *p*-phenylenediamines. Semipermanent hair colorants can be based on all three isomers of phenylenediamine.

Phenylenediamines are used in a variety of other applications, such as corrosion inhibitors, cross-linking agents for epoxy resins, toners for electrostatic image development (35), and to improve wrinkle resistance of cellulose acetate fibers (36).

The applications for *o*-phenylenediamines are limited but are useful for forming heterocyclic compounds and as analytical reagents for identifying a variety of functional groups.

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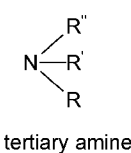
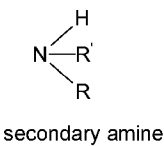
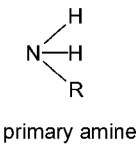
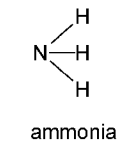
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AMINES BY REDUCTION

Amines are derivatives of ammonia in which one or more of the hydrogens is replaced with an alkyl, aryl, cycloalkyl, or heterocyclic group. When more than one hydrogen has been replaced, the substituents can either be the same or different. Amines are classified as primary, secondary, or tertiary depending on the number of hydrogens which have been replaced. It is important to note that the designations primary, secondary, and tertiary refer only to the number of substituents and not to the nature of the substituents as in some classes of compounds.

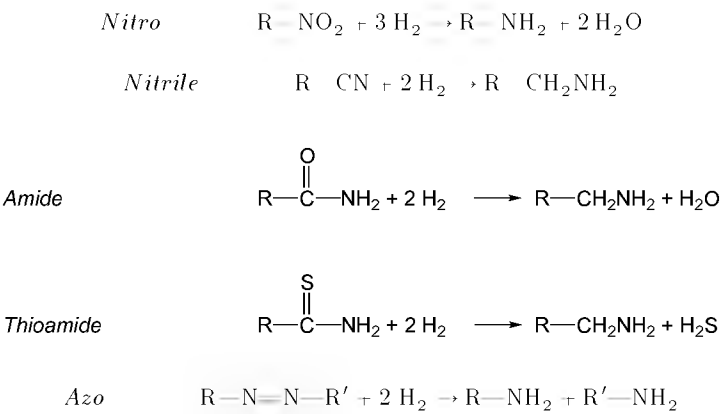


Amines can be prepared by a variety of methods including substitution reactions, rearrangements, ammonolysis, and reductions. On a large scale, however, ammonolysis and reductions are usually the most efficient and are generally used in commercial processes. In reductive methods, the nitrogen is already incorporated in the molecule, and the amine is formed by reducing the oxidation state of the compound with the addition of hydrogen. In theory, many different types of nitrogen-containing compounds can be reduced to amines. In practice, however, nitriles or nitro compounds are usually used because they are the most easily obtained starting materials.

There are several commercial processes for reducing nitro or nitrile groups to amines. Most large volume aromatic and aliphatic amines are made by continuous high pressure catalytic hydrogenation. Nitro compounds can also be reduced in good yields with iron and hydrochloric acid in the Buchamp process. The importance of the Buchamp process has declined over the last few decades, but it is still used in the pigment and dyestuff industry and to make iron oxide pigments; aniline is produced as a by-product. Other more specialized methods used for making amines by reduction include the Zinin reduction, in which sulfides in alkaline media are used to reduce aromatic nitro compounds, bisulfite reductions, electrochemical reductions, and reductions using metal amalgams or hydrides. The special case involving preparation of aliphatic amines by hydrogenation of aromatic amines is also included.

Catalytic Hydrogenation

In catalytic hydrogenation, a compound is reduced with molecular hydrogen in the presence of a catalyst. This reaction has found applications in many areas of chemistry including the preparation of amines. Nitro, nitroso, hydroxylamino, azoxy, azo, and hydrazo compounds can all be reduced to amines by catalytic hydrogenation under the right conditions. Nitriles, amides, thioamides, and oximes can also be hydrogenated to give amines (1). Some examples of these reactions follow:



Catalytic hydrogenation is the most efficient method for the large scale manufacture of many aromatic and aliphatic amines. Some of the commercially important amines produced by catalytic hydrogenation include aniline (from nitrobenzene), 1,6-hexanediamine (from adiponitrile), isophoronediamine (from 3-nitro-1,5,5-trimethylcyclohexanecarbonitrile), phenylenediamine (from dinitrobenzene), toluenediamine (from dinitrotoluene), toluidine (from nitrotoluene), and xylylidine (from nitroxylyene). As these examples suggest, aromatic amines are usually made by hydrogenating the

corresponding nitro compound, whereas the aliphatic amines generally start with the corresponding nitrile. The main reason for this difference is the availability of the necessary raw materials. Many aromatic hydrocarbons can be easily nitrated to give a variety of aromatic nitro compounds. For aliphatic amines, however, the nitrile precursor is generally easier to obtain than the corresponding aliphatic nitro compound. Nitriles, however, can only yield amines which are located at a primary carbon.

Catalytic hydrogenations can be carried out in the vapor phase or in the liquid phase, either with or without the use of a solvent. The vapor phase reaction is limited to compounds which are thermally stable and relatively volatile. High boiling compounds and those which are thermally unstable must be hydrogenated in the liquid phase.

Mechanism and Kinetics of Hydrogenation

Reduction of Nitro Compounds. The mechanism for catalytic hydrogenation of nitro compounds has been the subject of many investigations and there is much evidence that this reaction proceeds through several intermediate species. The most widely accepted mechanism for the hydrogenation of nitro compounds was proposed by Haber in 1898 (2) (see Fig. 1).

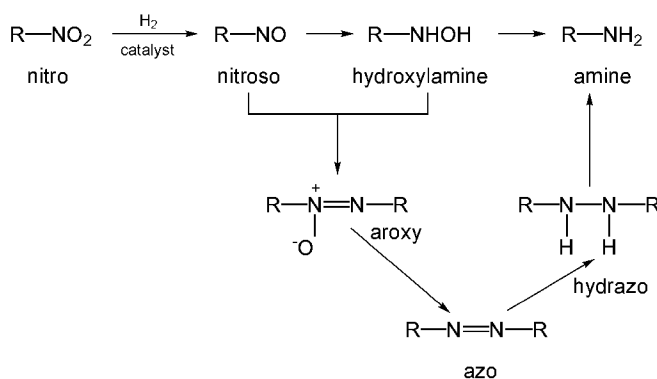


Fig. 1. Mechanism for the hydrogenation of nitro compounds. Functionalities are labeled.

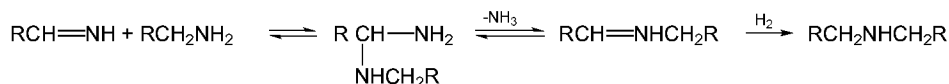
Haber based this mechanism on the electrochemical reduction of nitrobenzene, but it has since been used by many researchers to explain the results of hydrogenation studies. For example, a mechanistic and kinetic study of the hydrogenation of nitrobenzene to aniline concluded that the reaction proceeds through a number of intermediates including nitrosobenzene, phenylhydroxylamine, azoxybenzene, azobenzene, and hydrazobenzene, even though not all of these intermediates were detected (3). Further evidence of the existence of these intermediates is provided by reports that under certain conditions, catalytic hydrogenation of nitro compounds can yield either hydroxylamines (4,5) or azoxy compounds (6) as the major product.

Many kinetic studies on hydrogenation reactions of nitro compounds have been aimed at determining not only rate equations, but also the effect of various factors on the reaction rate. In one study, the vapor-phase hydrogenation of nitrobenzene to aniline using a copper oxide–chromium oxide catalyst was found to be half order with respect to hydrogen concentration and first order in nitrobenzene (7). Similarly, in a liquid-phase hydrogenation using a homogeneous catalyst, the reaction rate was found to be first order in nitrobenzene concentration and dependent on the hydrogen pressure (8). However, other workers have concluded that the order of the reaction with respect to the nitro compound can vary between 0 and 1, depending on factors such as the amount of catalyst and the nature of the solvent (9).

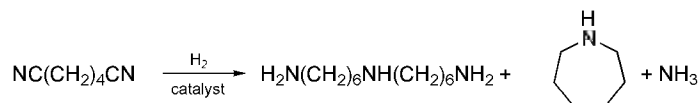
Reductions of Nitriles. In the reduction of nitriles, hydrogen is added progressively across the carbon–nitrogen triple bond, forming first the imine and then the amine.



One characteristic of this reaction that can cause problems is that secondary and tertiary amines are produced in addition to the primary amine. It has been proposed that these side reactions occur through reaction of the imine intermediate with the product amine, followed by the loss of ammonia and further hydrogenation (10).



The tertiary amine is formed in a similar manner from the imine and a secondary amine. This side reaction can be minimized by carrying out the hydrogenation in the presence of ammonia, which tends to shift the equilibrium back towards the imine. When a compound with two or more nitrile groups is hydrogenated, the formation of both cyclic and acyclic secondary and tertiary amines is possible, depending on whether the side reaction is intramolecular or intermolecular. For example, for the hydrogenation of adiponitrile:



Hydrogenation Raw Materials

Substrates. Many different types of nitrogen-containing compounds can be hydrogenated to amines, but nitro compounds and nitriles are the most commonly used starting materials.

Nitro Compounds. Many aromatic hydrocarbons react with nitric acid in the presence of sulfuric acid to form aromatic nitro compounds. The nitration reaction is an electrophilic aromatic substitution in which the orientation of the nitro group being introduced is controlled by the substituents which are already present (11). Because the nitro group is deactivating, each nitro group becomes progressively more difficult to add, and the reaction conditions can be controlled to give almost exclusively mono-, di- or trinitro compounds. For general reviews of nitration reactions see also references 12 and 13.

Nitriles. Nitriles can be prepared by a number of methods, including (1) the reaction of alkyl halides with alkali metal cyanides, (2) addition of hydrogen cyanide to a carbon–carbon, carbon–oxygen, or carbon–nitrogen multiple bond, (3) reaction of hydrogen cyanide with a carboxylic acid over a dehydration catalyst, and (4) ammoxidation of hydrocarbons containing an activated methyl group. For reviews on the preparation of nitriles see references 14 and 15.

Hydrogenation Catalysts. The key to catalytic hydrogenation is the catalyst, which promotes a reaction which otherwise would occur too slowly to be useful. Catalysts for the hydrogenation of nitro compounds and nitriles are generally based on one or more of the group VIII metals. The metals most commonly used are cobalt, nickel, palladium, platinum, rhodium, and ruthenium, but others, including copper (16), iron (17), and tellurium

(18) have been used. Despite this relatively small list, a wide variety of catalysts and catalyst modifications have been reported in the literature.

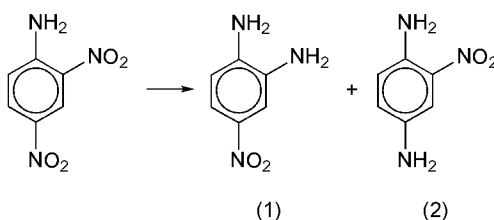
Physical Characteristics. Heterogeneous catalysts are generally used for both large and small scale hydrogenations, but many homogeneous catalysts have also been used. Homogeneous and heterogeneous catalysts generally contain the same type of metals, but in homogenous catalysts the metals are present in the form of complexes or clusters with various organic and inorganic ligands. Some of the homogeneous catalysts which have been reported include copper triphenylphosphine complexes (19), ruthenium phosphine complexes (20,21), rhodium carbonyl clusters (8), and complexes of palladium with quinoline (22), pyridine (23,24), and phenylisocyanate (25) ligands. Despite the high activity (20) and selectivity (21) sometimes claimed for homogeneous catalysts, heterogeneous catalysts are usually preferred because they are easy to use and recover for reuse.

Heterogeneous hydrogenation catalysts can be used in either a supported or an unsupported form. The most common supports are based on alumina, carbon, and silica. Supports are usually used with the more expensive metals and serve several purposes. Most importantly, they increase the efficiency of the catalyst based on the weight of metal used and they aid in the recovery of the catalyst, both of which help to keep costs low. When supported catalysts are employed, they can be used as a fixed bed or as a slurry (liquid phase) or a fluidized bed (vapor phase). In a fixed-bed process, the amine or amine solution flows over the immobile catalyst. This eliminates the need for an elaborate catalyst recovery system and minimizes catalyst loss. When a slurry or fluidized bed is used, the catalyst must be separated from the amine by gravity (settling), filtration, or other means.

The available surface area of the catalyst greatly affects the rate of a hydrogenation reaction. The surface area is dependent on both the amount of catalyst used and the surface characteristics of the catalyst. Generally, a large surface area is desired to minimize the amount of catalyst needed. This can be accomplished by using either a catalyst with a small particle size or one with a porous surface. Catalysts with a small particle size, however, can be difficult to recover from the material being reduced. Therefore, larger particle size catalyst with a porous surface is often preferred. A common example of such a catalyst is Raney nickel.

Because of its relatively low cost, high activity, and long life, Raney nickel is one of the most commonly used hydrogenation catalysts. Raney nickel is composed primarily of nickel and aluminum which has been processed to give it a large surface area. This is done by activating an alloy of nickel and aluminum with aqueous sodium hydroxide under controlled conditions to dissolve most of the aluminum, leaving behind the nickel. The resulting catalyst is extremely porous, having a surface area of up to 100 m² g (26). There are several standard types of Raney nickel which are prepared using different activation conditions. These differ both in their physical characteristics and in their activity. Similar activation processes have also been applied to other metals to increase their surface area and catalytic activity.

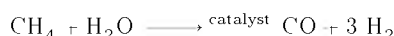
Activity and Selectivity. The activity of a catalyst refers to its ability to promote the desired reaction whereas the selectivity relates to how effective a catalyst is at promoting only a specific reaction. The selectivity which is required in a particular hydrogenation depends on the functional groups present in the material being hydrogenated. Many common functional groups can be reduced by catalytic hydrogenation with varying degrees of difficulty, and often one functional group must be reduced selectively in the presence of other groups which are to be left unchanged. For example, in the reduction of aromatic nitro compounds the catalyst and reaction conditions must be selected so that the nitro group is completely reduced while the aromatic ring is left intact. Since aromatic rings are generally much more difficult to reduce than nitro groups, this reduction can be carried out very selectively. However, other cases exist where it is much harder to selectively reduce one functional group in the presence of another. An impressive example of the selectivity which can be achieved is in the reduction of 2,4-dinitroaniline [97-02-9], (C₆H₅N₃O₄). Not only is it possible to reduce one of the nitro groups to an amine while leaving the other unchanged, but through proper choice of catalyst and reaction conditions, either 4-nitro-1,2-benzenediamine [99-56-9] (1) (C₆H₇N₃O₂) (27) or 2-nitro-1,4-benzenediamine [5307-14-2] (2) (28) can be made in good yield.



The subject of catalyst selection for hydrogenation reactions has been summarized in several books (29,30).

Poisoning and Deactivation. Many catalysts can be inhibited or poisoned by the presence of certain materials. Sulfur, phosphorus, arsenic, and bismuth compounds that have unshared electrons are common catalyst poisons. They act by binding to the catalyst surface, thereby preventing the desired reaction from occurring. Catalysts can also be deactivated by other means including pore plugging and physical degradation. However, the effects of poisoning or deactivation are not always permanent, and the catalyst can sometimes be regenerated. For a review of catalyst poisoning, deactivation and regeneration, see reference 31.

Hydrogen. Most large scale industrial processes operate with essentially pure hydrogen, but hydrogen mixed with carbon monoxide or inert gases can also be used. Hydrogen can be obtained by any of several known processes (32), but those which simultaneously produce carbon monoxide as a by-product are often favored. The carbon monoxide can react with chlorine to form phosgene, the principal reagent required to convert amines to isocyanates. Methane gas is a convenient starting material for hydrogen generation, and the hydrogen and carbon monoxide produced from methane are generally of a high purity. One common route which produces hydrogen and carbon monoxide from methane is steam reforming, in which methane gas and steam are passed over a nickel–magnesia catalyst at about 800°C under pressure:



Solvents. A solvent is not always required in catalytic hydrogenations, but the use of a solvent can have several benefits. Using a solvent can make it simpler to hydrogenate solids or materials which are otherwise difficult to handle. A solvent can also act to moderate the heat of reaction, which can be quite large. Finally, a solvent can affect the course of a reaction by influencing the selectivity of the hydrogenation (33). Since hydrogenation processes usually operate under high pressure, the reaction temperature can be significantly above the normal boiling point of the solvent. In practice, low molecular weight alcohols, particularly methanol or ethanol, are the most commonly used hydrogenation solvents. Other solvents which have been used include acetic acid, acetone, ammonia, benzene, glycerol, ethylene glycol, hydrochloric acid, sulfuric acid, and water. When applicable the hydrogenation product itself can act as a solvent (34).

Additives. Several literature references and patents deal with the use of additives to promote or suppress particular reactions during the preparation of amines by catalytic hydrogenation. For example, the use of triethyl phosphite [122-52-1] (35), phosphoric acid [7664-38-2] (36), and 2,2'-thiodiethanol [111-48-8] C₄H₁₀O₂S (37) has been reported to suppress dehalogenation during the reduction of halogen containing aromatic nitro compounds. Additives have also been reported to be useful both in suppressing the formation of amidines during the hydrogenation of nitriles (38) and promoting the reduction of aromatic nitrosulfonic acids to the corresponding amino derivatives (39). The presence of ammonia as an additive or solvent during the hydrogenation of nitriles helps to inhibit the formation of secondary and tertiary amine by-products.

Hydrogenation Reaction Conditions

Heat of Reaction and Heat Transfer. Catalytic hydrogenation is a very exothermic reaction and, therefore, removal of the heat generated is an important consideration in any hydrogenation process. For example, the heat of reaction for the catalytic hydrogenation of nitroxylenes to xylenediamines is about 488 kJ/mol (117 kcal/mol) at 200°C (40). This value is comparable to the 544 kJ/mol (130 kcal/mol), which is often quoted for the hydrogenation of nitrobenzene to aniline. By comparison, the heat of reaction for the hydrogenation of nitriles is much smaller, about 310 kJ/mol (74 kcal/mol) for the hydrogenation of adiponitrile to 1,6-hexanediamine (41). This difference is, in part, because water is formed in the hydrogenation of nitro compounds, but not in the hydrogenation of nitriles. Nevertheless, any hydrogenation process must be able to remove sufficient heat to keep the reaction mixture at the desired temperature.

Temperature and Pressure. Temperature and pressure both have large effects on the course of a hydrogenation process. Higher

temperatures lead to faster reactions, but excessive temperatures can result in undesirable by-products and unsafe conditions. A study of the hydrogenation of 3,4-dichloroaniline showed that this reaction involved the initial formation of the hydroxylamine, which at low temperatures disproportionates to give the amine and the nitroso compound. At high temperatures, however, a highly exothermic reaction occurs in which the hydroxylamine and nitroso compounds form the azoxy compound (42).

Increasing hydrogen pressure also increases the rate of reaction by increasing the contact between the hydrogen gas, the catalyst, and the substrate which is needed for the reaction to take place. Usually higher pressures do not cause the problems associated with high temperatures. In fact, increasing the hydrogen pressure may actually serve to suppress side reactions which can occur under hydrogen deficient conditions (43).

Mixing. Agitation also plays a large role in optimizing a hydrogenation process. The metal catalyst is often much heavier than the rest of the reaction mixture and therefore vigorous mixing is needed to keep the catalyst in contact with the material being reduced and the hydrogen. Various methods have been used to achieve this mixing. With a fixed-bed catalyst system, the reactants flow through the stationary catalyst. In a fluidized-bed reactor the upward vapor flow keeps the catalyst suspended, ensuring good contact. A similar effect is possible with a liquid slurry, where the flow of liquid and gas keeps the catalyst and reactants mixed. It has also been reported that pulsation at frequencies of 30 to 3000 Hz can provide the necessary mixing when the liquid phase hydrogenation is carried out in tube reactors (44). More conventional agitators can also be used in stirred reactors, and in the laboratory the entire reactor is sometimes shaken to provide the necessary mixing.

Industrial Hydrogenation Processes

Liquid-Phase Hydrogenation of Nitro Compounds. Most high boiling aromatic amines are prepared by liquid-phase hydrogenation of the corresponding nitro compound, either with or without the use of a solvent. Early catalytic hydrogenations were performed in stirred batch reactors. More recently these have been replaced by continuous processes which provide better control in terms of heat transfer and mixing of the reactants. A continuous liquid-phase hydrogenation process is illustrated by the process for toluenediamine. Toluene can be readily nitrated by conventional means to give dinitrotoluene (DNT) (methyl dinitrobenzene [25321-14-6], $C_7H_7N_2O_4$), consisting primarily of the 2,4- and 2,6-isomers in a ratio of about 4:1 (45). The DNT can be reduced by high pressure liquid-phase catalytic hydrogenation to the corresponding toluenediamine (TDA) (ar-methylbenzenediamine [25376-45-8], $C_7H_{10}N_2$) (see AMINES, AROMATIC, DIAMINOTOLUENES). Most of the TDA produced is phosgenated to give toluenediisocyanate (TDI) (diisocyanatomethylbenzene [26471-62-5], $C_9H_8N_2O_2$), which is used in the manufacture of polyurethanes. A typical industrial process for the reduction of DNT to TDA, as described by patents, is shown in Figure 2 and described in the following (46,47).

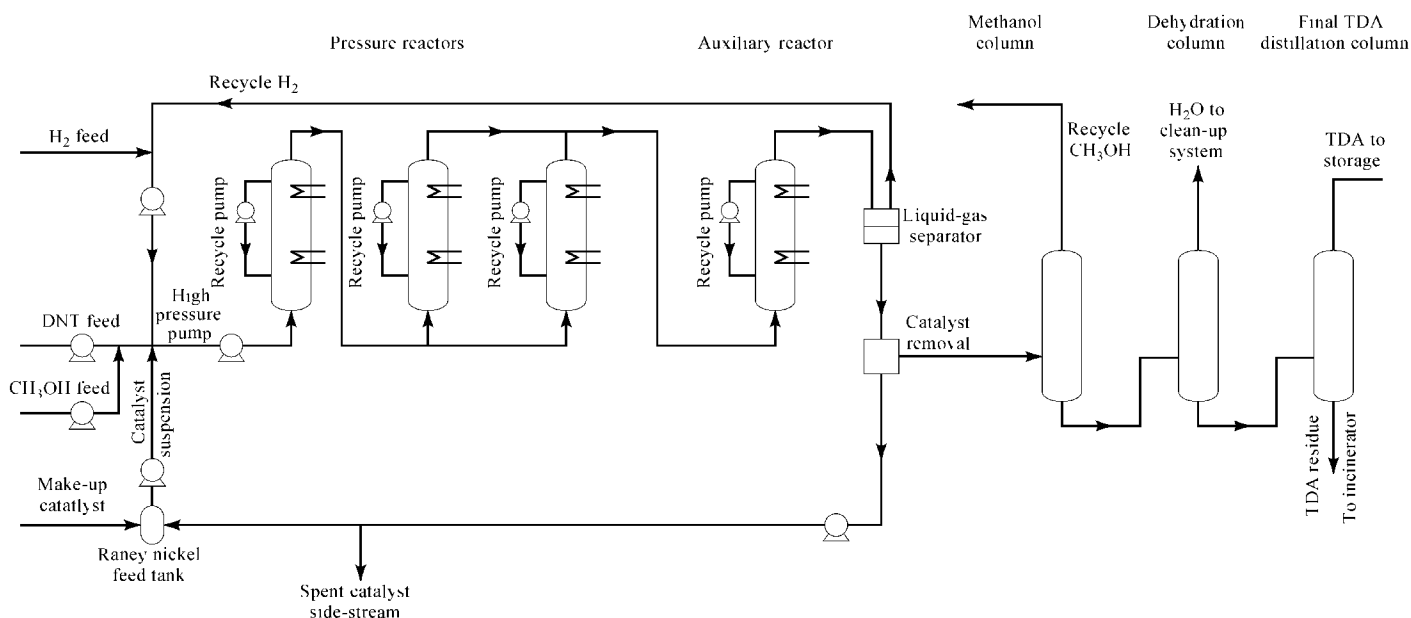


Fig. 2. Continuous liquid phase reduction of dinitrotoluene.

A solution containing about 25% DNT in methanol is pumped along with a Raney nickel slurry and enough hydrogen gas to complete the reaction through a series of reactors. There are three high pressure reactors plus an auxiliary reactor, each with a volume of approximately 450 L. The reactors are about 6 m long and 35 cm in diameter and are equipped with water cooling for temperature control. This reaction mixture is fed to the first reactor at a rate of approximately 2000 kg/h. The material from the first reactor is split and fed to the second and third reactors, which are run in parallel. The temperature of the reactors is maintained at about 100°C and the hydrogen pressure at between 15,000 and 20,000 kPa (150 and 200 atm). After the reaction is completed, the pressure is reduced and the excess hydrogen removed in a liquid–gas separator. The hydrogen is recycled to the beginning of the process and the product stream continues on through a series of catalyst removal steps. The recovered catalyst is also recycled with only a small amount, generally 0.1 to 0.3%, being lost in the process. After the catalyst is removed, the product is sent to a methanol column where the solvent is removed and recycled. The water is then removed in the dehydration column. The recovered water from this step contains volatile amines and other by-products and must be processed further before it can be recycled or discharged to the waste treatment plant. The product from the dehydration column can be used directly or taken to a final TDA column where it is distilled to give a product which is more than 99% pure. The residue from the final column can be disposed of by incineration or processed to recover some of the amine, thereby improving the yield and reducing waste-disposal problems.

Numerous modifications to the above process are possible and many variations have been suggested. Inert solvents other than methanol can be used; however, low molecular weight alcohols are usually considered preferable. Part of the reaction product can be recycled back to the front of the process to reduce the amount of solvent required and to eliminate problems associated with DNT solidification. A 76:24 mixture of DNT:TDA has been found to exhibit a minimum freezing point of 26°C, as compared to 50°C for pure DNT (46,47). The temperature at which the reaction is carried out can also be varied. Higher temperatures not only reduce the reaction time needed, but also result in less residue being formed (46). A temperature of 115 to 130°C is considered ideal, whereas temperatures above 170°C are considered unsafe.

Vapor Phase Hydrogenations of Nitro Compounds. Catalytic hydrogenation of nitro compounds can be carried out in the vapor phase, provided the boiling point of the compound is low enough and the material is thermally stable. These two conditions effectively limit this process to aliphatic and relatively simple aromatic nitro compounds such as nitrobenzene or nitroxyline. Early vapor-phase hydrogenation processes used fixed-bed catalysts. However, fluidized-bed catalytic vapor-phase hydrogenations, such as the one illustrated by the process for aniline, have become more common (see AMINES, AROMATIC, ANILINE AND DERIVATIVES).

Nitrobenzene [98-95-3], $C_6H_5NO_2$ is produced by the nitration of benzene with a mixture of nitric and sulfuric acid. A process for the manufacture of aniline [62-53-3], C_6H_7N , from nitrobenzene is shown in Figure 3 (16). Nitrobenzene, which contains less than 10 ppm nitrothiophene, a catalyst poison, is fed to a vaporizer where it is vaporized. As the gaseous nitrobenzene leaves the vaporizer, it is mixed with a 200% excess of hydrogen gas. The gaseous mixture then passes upward through a porous distributor plate into the reduction chamber of the fluidized-bed reactor which contains the

silica-supported copper catalyst. The catalyst powder is carried upward through the reactor by the vapor flow. The vapor velocity through the reactor is about 30 cm s. The reaction occurs at 270°C and 234 kPa (2.3 atm) with a very short contact time. The excess heat of reaction is removed by circulating heat transfer fluid through cooling tubes located in the catalyst bed. The upper portion of the reactor is large enough to allow most of the catalyst to fall back into the main catalyst bed. Any catalyst which escapes from the reactor is removed from the product by stainless steel filters.

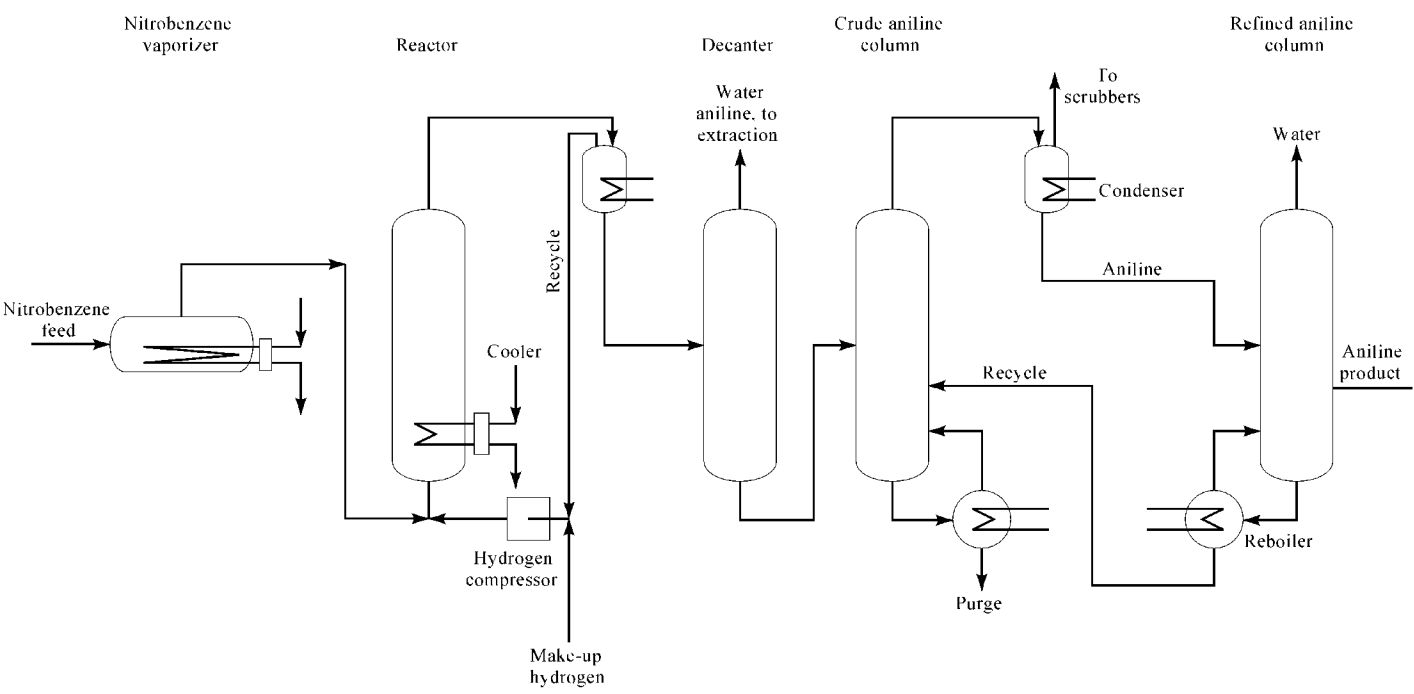


Fig. 3. Continuous fluidized-bed vapor phase reduction of nitrobenzene.

After leaving the reactor, the reaction mixture consisting of aniline, water, and excess hydrogen is cooled and condensed prior to the purification steps. First, the excess hydrogen is removed and recycled back to the reactor. The rest of the mixture is sent to the decanter where the water and aniline are separated. The crude aniline, which contains less than 0.5% of unreacted nitrobenzene and about 5% water, is distilled in the crude aniline column. The aniline is further dehydrated in the finishing column to yield the purified aniline. Meanwhile, the aqueous layer from the decanter, which contains about 3.5% aniline, is extracted to recover the aniline and clean up the water before it is sent to the waste-water treatment plant.

This process produces aniline with a yield of greater than 99% of theory. The appearance of nitrobenzene in the product is a sign of catalyst deactivation and the catalyst must be regenerated. This is done by stopping the nitrobenzene and hydrogen flow, and passing air through the catalyst at temperatures between 250 and 350°C. With regeneration, each gram of catalyst can produce a minimum of 600 grams of aniline before it must be replaced.

Aliphatic Amines from the Hydrogenation of Nitriles One of the most common and economical means of producing aliphatic amines is by the catalytic hydrogenation of nitriles, eg, the process for 1,6-hexanediamine. Adiponitrile (hexanedinitrile [111-69-3], $C_6H_8N_2$), is produced commercially by several routes which are based on different raw materials. It can be made by reaction of adipic acid (qv) with ammonia over a catalyst or by the dimerization of acrylonitrile (qv) at the cathode in an electrolytic cell. Adiponitrile is also made from butadiene, either by direct reaction with hydrogen cyanide or by first chlorinating the butadiene to give 1,4-dichlorobutane, which then reacts with sodium cyanide. A continuous process for the reduction of adiponitrile to 1,6-hexanediamine ([124-09-4], $C_6H_{16}N_2$), is illustrated in Figure 4 and described below (41). This process uses a fixed-bed catalyst with liquid ammonia as a solvent to suppress formation of secondary and tertiary amines.

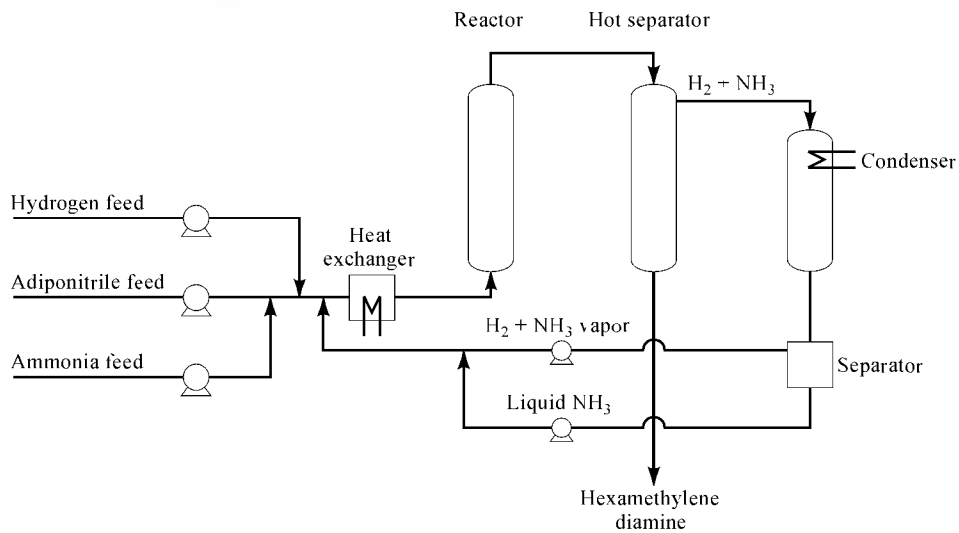


Fig. 4. Continuous fixed-bed reduction of adiponitrile to 1,6-hexanediamine.

Adiponitrile, liquid ammonia, and hydrogen gas are introduced together in a molar ratio of approximately 1:25:38 under a pressure of about 60 MPa (600 atm). The mixture passes through a preheater where the temperature is raised to about 30°C below the desired reaction temperature. The mixture then enters the reactor which contains the catalyst in the form of a fixed bed. Several different catalysts can be used, including copper–cobalt, cobalt–aluminum, cobalt oxide, and chromium oxide–cobalt oxide. The preferred temperature range is from 110 to 135°C, but any temperature between 100 and 150°C can be used. The adiponitrile is converted to 1,6-hexanediamine in the reactor and transferred to the hot separator where the gaseous hydrogen and ammonia are removed. The hydrogen and ammonia are then taken to a condenser for recycling while the diamine is taken forward for purification.

About 310 kJ mol (75 kcal mol) of heat is released during this reaction and the exotherm is controlled by adjusting the recycle streams. Part of the heat is used to raise the temperature of the reaction mixture the final 30°C while a large amount of heat is expended in vaporizing the ammonia.

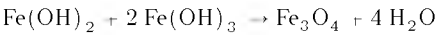
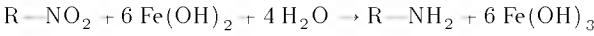
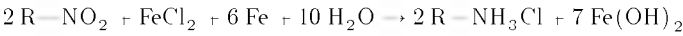
Büchamp Process

In the Büchamp process, nitro compounds are reduced to amines in the presence of iron and an acid. This is the oldest commercial process for preparing amines, but in more recent years it has been largely replaced by catalytic hydrogenation. Nevertheless, the Büchamp reduction is still used in the dyestuff industry for the production of small volume amines and for the manufacture of iron oxide pigments; aniline is produced as a by-product. The Büchamp reduction is generally run as a batch process; however, it can also be run as a continuous (48) or semicontinuous process (49).

Reaction Mechanism. The overall reaction in the Büchamp process is as follows



However, this is an oversimplification, and the Büchamp reduction is a complex reaction which can be better represented by the following stepwise mechanism (50).



In this representation the FeCl₂ which takes part in the first step of the reaction is not a true catalyst, but is continuously formed from HCl and iron. This is a highly exothermic process with a heat of reaction of 546 kJ mol (130 kcal mol) for the combined charging and reaction steps (50). Despite the complexity of the Büchamp process, yields of 90–98% are often obtained. One of the major advantages of the Büchamp process over catalytic hydrogenation is that it can be run at atmospheric pressure. This eliminates the need for expensive high pressure equipment and makes it practical for use in small batch operations. The Büchamp process can also be used in the laboratory for the synthesis of amines when catalytic hydrogenation cannot be used (51).

Some of the important parameters in the Büchamp process are the physical state of the iron, the amount of water used, the amount and type of acid used, agitation efficiency, reaction temperature, and the use of various catalysts or additives. When these variables are properly controlled, the amine can be obtained in high yields while controlling the color and physical characteristics of the iron oxide pigment which is produced.

Raw Materials.

Iron. Clean, finely divided, soft, gray cast iron yields the best results. In practice, the iron is often etched by heating it in an acid solution prior to addition of the nitro compound. This ensures a good iron surface and prevents the possibility of a violent delayed reaction. Since the rate of reaction depends in part on the surface area of the iron, finely divided iron leads to a smoother reaction requiring less time. When coarse iron is used, the reaction is slower and a larger excess of iron is required to complete the reaction. For these reasons, iron turnings, shavings, or borings are generally preferred. It has been reported that impurities in the iron can lead to undesirable side reactions in certain cases. For example, when ring-chlorinated aromatic nitro compounds are reduced, dechlorination is possible. Dechlorination is promoted by the presence of nickel in the iron (52), but can be retarded by addition of certain inhibitors including potassium thiocyanate and dicyandiamide (53,54).

Water. Based on the overall balanced equation for this reaction, a minimum of one mole of water per mole of nitro compound is required for the reduction to take place. In practice, however, 4 to 5 moles of water per mole of nitro compound are used to ensure that enough water is present to convert all of the iron to the intermediate ferrous and ferric hydroxides. In some cases, much larger amounts of water are used to dissolve the amino compound and help separate it from the iron oxide sludge after the reaction is complete.

Acid. The reaction requires only enough acid to generate the ferrous ion which is needed to participate in the first step. Alternatively, a ferrous salt can be added directly. Generally 0.05 to 0.2 equivalents of either hydrochloric or sulfuric acid is used, but both acids have their drawbacks. Hydrochloric acid can cause the formation of chlorinated amines and sulfuric acid can cause the rearrangement of intermediate arylhydroxylamines to form hydroxyaryl amines. Occasionally an organic carboxylic acid such as acetic or formic acid is used when there is a danger of hydrolysis products being formed.

Reaction Conditions.

Mixing. Because of the heterogeneous nature of this system, efficient mixing is essential to ensure the intimate contact of the iron, nitro compound, and water soluble catalyst. An agitator which allows the iron to settle to the bottom and the other materials to separate into layers does not function efficiently. On the other hand, a reaction whose rate is limited by the quality of the iron will not be significantly improved by better mixing.

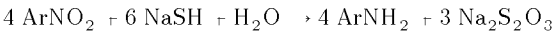
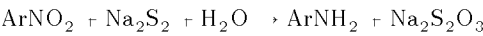
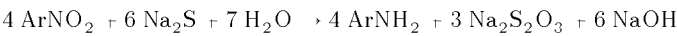
Amine Recovery. Once the reaction is completed, the amine must be separated from the iron oxide sludge. First, the iron oxide is allowed to settle and the liquid amine layer is removed by siphoning or decanting. A significant amount of amine remains in the iron oxide and this must also be recovered. Several methods have been used to accomplish this (55). Either steam distillation or vacuum distillation of the amine from the iron oxide is possible. In steam distillation, steam is fed into the iron oxide sludge and the condensate is collected. This is an effective but expensive method of recovering the amine. Vacuum distillation is less expensive than steam distillation, but it is difficult to recover all of the amine from the iron oxide using vacuum distillation. Filtration is another way of recovering the amine from the iron oxide. In this method, the iron oxide is first washed with water recovered from the amine purification. This is followed by fresh boiling water and finally, the iron oxide is blown with hot air or steam to remove the remaining liquid.

Preparation of Aniline by the Büchamp Process. About 1500 L of a ferrous chloride solution and 1300–1500 L of aniline water are charged to a 20,000-L reactor. Because of the abrasive nature of this reaction mixture, the reactor is often lined with tile or contains a replaceable liner. To this mixture are added 1000 kg of iron filings and 300 L of nitrobenzene. Once the reaction is underway, an additional 4700 kg of nitrobenzene and 5300 kg of iron are added together over a period of 6 to 9 h. After about 12 h, the reaction is complete and the mixture is neutralized. Then the iron sludge is allowed to settle and the aniline is decanted off through an adjustable dip tube. The iron oxide sludge is steam distilled by passing steam through it for 4–5 h and the condensate collected. The condensate is added to the aniline which was decanted and the material is further neutralized and purified by distillation. The aniline water from the distillation is returned to the process or extracted with nitrobenzene to recover the residual aniline (56).

Several modifications to this process are possible (55). Instead of adding ferrous chloride directly, it is more common to generate it by using iron and hydrochloric acid. The order in which the reactants are added can also be altered, and it is even possible to add all of the iron or aniline at the beginning of the reaction. There are also other ways to recover the aniline from the iron oxide sludge.

Miscellaneous Reductions

Zinin Reduction. The method of reducing aromatic nitro compounds with divalent sulfur is known as the Zinin reduction (57). This reaction can be carried out in a basic media using sulfides, polysulfides, or hydrosulfides as the reducing agent. These reactions can be represented as follows when the counter ion is sodium:

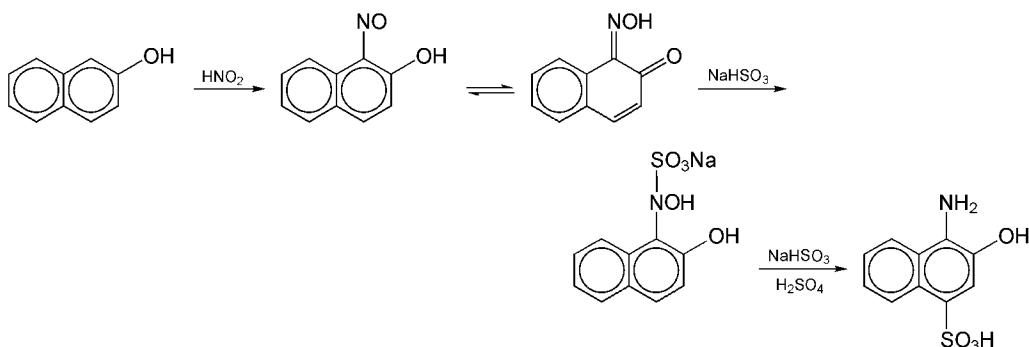


Although this reduction is more expensive than the Büchamp reduction, it is used to manufacture aromatic amines which are too sensitive to be made by other methods. Such processes are used extensively where selectivity is required such as in the preparation of nitro amines from dinitro compounds, the reduction of nitrophenol and nitroanthraquinones, and the preparation of aminoazo compounds from the corresponding nitro derivatives. Amines are also formed under the conditions of the Zinin reduction from aromatic nitroso and azo compounds.

The Zinin reduction is also useful for the reduction of aromatic nitro compounds to amines in the laboratory. It requires no special equipment, as is the case with catalytic hydrogenations, and is milder than reductions with iron and acid. Usually ammonium or alkali sulfides, hydrosulfides or polysulfides are used as the reactant with methanol or ethanol as the solvent.

The reduction of *m*-dinitrobenzene [99-65-0] to *m*-nitroaniline [99-09-2] on a laboratory scale offers an example. A solution containing 18 g of sodium sulfide and 6 g of sodium bicarbonate in 50 mL of water is prepared, mixed with 50 mL of methanol, and filtered to remove precipitated sodium carbonate. Next, 6.7 g of *m*-dinitrobenzene, C₆H₄N₂O₄, in 50 mL of methanol is added and the mixture refluxed for 20 min. The methanol is removed by distillation and the residue poured into cold water where it solidifies. The material can then be recrystallized from 75% aqueous methanol to give a 69% yield of *m*-nitroaniline, C₆H₅N₂O₂, with a melting point of 114°C (58).

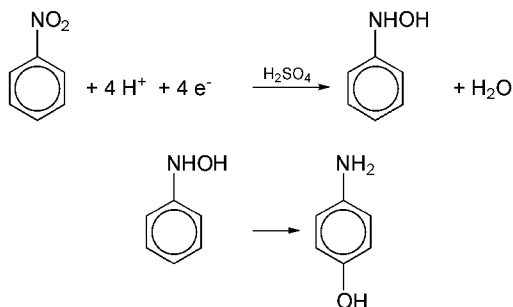
Sodium Bisulfite. Sodium bisulfite [7631-90-5], NaHSO₃, is occasionally used to perform simultaneous reduction of a nitro group to an amine and the addition of a sulfonic acid group. For example, 4-amino-3-hydroxyl-1-naphthalenesulfonic acid [116-63-2], C₁₀H₉NO₄S, is manufactured from 2-naphthol in a process which uses sodium bisulfite (59). The process involves nitrosation of 2-naphthol in aqueous medium, followed by addition of sodium bisulfite and acidification with sulfuric acid.



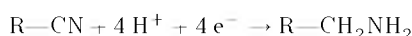
Electrolytic Reductions. Both nitro compounds and nitriles can be reduced electrochemically. One advantage of electrochemical reduction is the cleanness of the operation. Since there are a minimum of by-products, both waste disposal and purification of the product are greatly simplified. However, unless very cheap electricity is available, these processes are generally too expensive to compete with the traditional chemical methods.

Nitro Compounds. When nitro compounds are reduced by electrochemical methods a number of products are possible depending on such factors as the nature of the electrode, the electrode potential, and the reaction media. For the reduction of nitrobenzene these products include aniline, *p*-aminophenol, *p*-chloroaniline, phenylhydroxylamine, azoxybenzene, azobenzene, and hydrazobenzene (60).

Electrolytic reductions generally cannot compete economically with chemical reductions of nitro compounds to amines, but they have been applied in some specific reactions, such as the preparation of aminophenols (qv) from aromatic nitro compounds. For example, in the presence of sulfuric acid, cathodic reduction of aromatic nitro compounds with a free para-position leads to *p*-aminophenol [123-30-8] by rearrangement of the intermediate *N*-phenyl-hydroxylamine [100-65-2] (61).



Nitriles. The electrolytic reduction of nitriles requires a high negative potential, but can lead to amines in good yields under the right conditions. This reaction occurs in acidic media according to the following equation (62).



In general, however, the electrochemical reduction of nitriles offers no significant advantages over traditional chemical methods and has not been widely used.

Metal Amalgams and Hydrides. Metal hydrides and amalgams are sometimes the preferred method of reducing various functional groups in the laboratory, especially when the necessary equipment for catalytic hydrogenations is unavailable. However, these reagents are usually too expensive to make their use on a large commercial scale feasible.

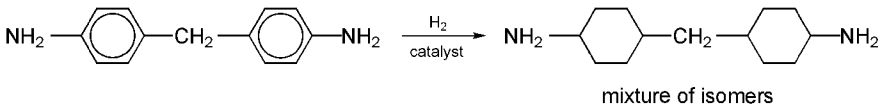
Metal Amalgams. Alkali metal amalgams function in a manner similar to a mercury cathode in an electrochemical reaction (63). However, it is more difficult to control the reducing power of an amalgam. In the reduction of nitro compounds with an NH₄(Hg) amalgam, a variety of products are possible. Aliphatic nitro compounds are reduced to the hydroxylamines, whereas aromatic nitro compounds can give amino, hydrazo, azo, or azoxy compounds.

Metal Hydrides. Metal hydrides can sometimes be used to prepare amines by reduction of various functional groups, but they are seldom the preferred method. Most metal hydrides do not reduce nitro compounds at all (64), although aliphatic nitro compounds can be reduced to amines with lithium aluminum hydride. When aromatic amines are reduced with this reagent, azo compounds are produced. Nitriles, on the other hand, can be reduced to amines with lithium aluminum hydride or sodium borohydride under certain conditions. Other functional groups which can be reduced to amines using metal hydrides include amides, oximes, isocyanates, isothiocyanates, and azides (64).

Aliphatic Amines from the Ring Reduction of Aromatic Amines. Certain aliphatic amines can be prepared by reduction of aromatic amines by catalytic hydrogenation. This method is applicable only when a corresponding aromatic amine is available. Nevertheless, it is used for the production of several important amines including cyclohexylamine and bis(4-aminocyclohexyl)methane. Reduction of an aromatic ring can be carried out using the same types of catalysts that are used for the hydrogenation of nitro compounds and nitriles. The conditions required are much harsher, however, and higher temperatures and pressures are generally required.

Bis(4-aminocyclohexyl)methane. Aniline can react with formaldehyde in the presence of an acid catalyst to give a mixture of polymeric amines. The principal component of this mixture is 4,4'-diaminodiphenylmethane (4,4'-methylenebisbenzenamine [101-77-9], C₁₃H₁₄N₂). Most of this material is used in the production of isocyanates for polyurethanes. However, part of the 4,4'-diaminodiphenylmethane is converted to bis(4-aminocyclohexyl)methane (4,4'-methylenebiscyclohexanamine [1761-71-3], C₁₃H₂₂N₂) by catalytic hydrogenation, which results in a mixture of cis,cis-, cis,trans-, and trans,trans-stereoisomers. Typically a ruthenium catalyst is used at relatively high temperatures and pressures. For example, one patent describes a process for preparation of bis(4-aminocyclohexyl)methane from 4,4'-diaminodiphenylmethane with excellent yields in short times (65). The reaction is carried out using any of several ruthenium catalysts in the presence of a solvent and ammonia. The preferred temperature range is 225 to

250°C with an initial hydrogen pressure of about 14 to 24 MPa (140–240 atm). Under these conditions, the reaction is completed in less than 30 min with yields of 93 to 97% or higher.



Intermediates from the Reduction of Nitro Compounds

In the reduction of nitro compounds to amines, several of the intermediate species are stable and under the right conditions, it is possible to stop the reduction at these intermediate stages and isolate the products (see Figure 1, where R = C₆H₅). Nitrosobenzene [586-96-9], C₆H₅NO, can be obtained by electrochemical reduction of nitrobenzene [98-95-3]. Phenylhydroxylamine, C₆H₅NHOH, is obtained when nitrobenzene reacts with zinc dust and calcium chloride in an alcoholic solution. When a similar reaction is carried out with iron or zinc in an acidic solution, aniline is the reduction product. Hydrazobenzene [122-66-7], C₁₂H₁₂N₂, is formed when nitrobenzene reacts with zinc dust in an alkaline solution. Azoxybenzene [495-48-7], C₁₂H₁₀N₂O, is formed from two molecules of nitrobenzene when heated in an alcoholic solution containing a strong base such as sodium hydroxide. Azobenzene [103-33-3], C₁₂H₁₀N₂, can be obtained by distilling azoxybenzene in the presence of iron powder or by reaction of nitrobenzene with sodium stannite [12214-41-7], Na₂SnO₂.

Environmental and Safety Aspects

Amines, nitro compounds, nitriles, and the various solvents and reagents used in the preparation of amines by reduction vary widely in the hazards they may pose. Some of these materials are acutely toxic by ingestion, inhalation, or absorption through the skin. Others are skin irritants or sensitizers. Still others may cause damage by chronic exposure to organs, such as the liver, or may be carcinogenic. Since amines vary so widely in their potential danger, no general rules can govern their safe use in all cases. The Material Safety Data Sheet (MSDS) for the material in question should be consulted before the chemicals are used.

Waste Treatment and Effluent Monitoring. Modern chemical plants are closed systems to prevent the emission of pollutants into the environment. Vents are protected by fume scrubbers and process waste water is cleaned up before being discharged. Any unavoidable by-products are collected and disposed of in a manner consistent with government regulations. In the water treatment plant diagrammed in Figure 5, the incoming water is first treated to neutralize the normally acidic stream and the solids are removed in a 4 million liter clarifier. Biological treatment then removes many of the the organic compounds. Aniline and methanol are readily removed at this stage; nitro compounds are much more difficult for the bacteria to digest. An activated carbon system removes final traces of organics and much of the remaining color, providing an effluent which meets state and federal regulations. The carbon is routinely regenerated in a system that incinerates the organics absorbed from the waste stream. Finally, the water leaving the waste water treatment plant is monitored by chemical and biological tests to ensure its quality.

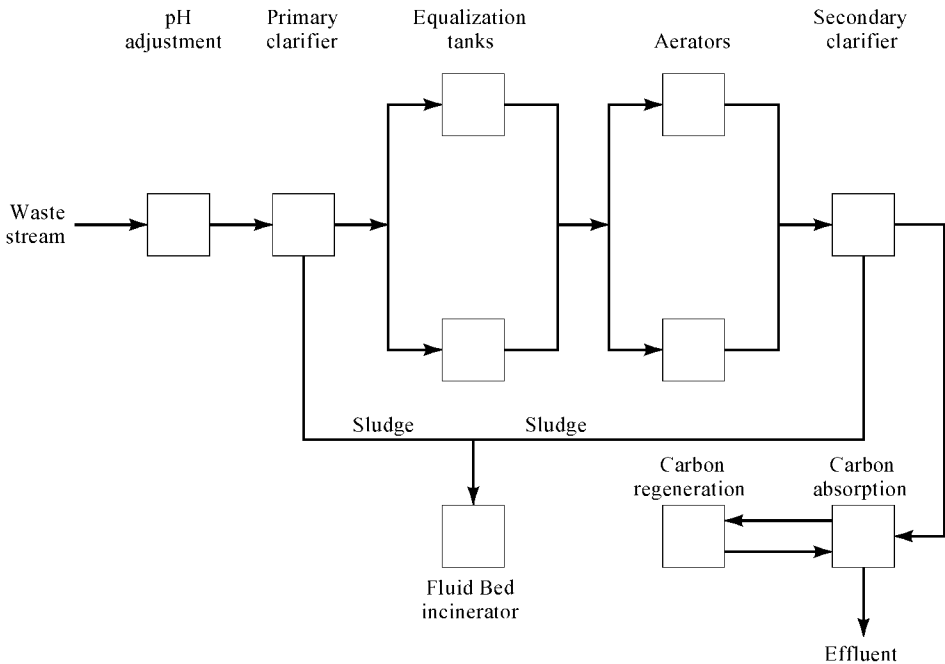


Fig. 5. Typical industrial waste-water treatment plant, eg, 25 × 10⁶ L day⁻¹, Mobay Corporation plant at New Martinsville, W.V. (66).

Air Monitoring. The atmosphere in work areas is monitored for worker safety. Volatile amines and related compounds can be detected at low concentrations in the air by a number of methods. Suitable methods include chemical, chromatographic, and spectroscopic techniques. For example, the NIOSH Manual of Analytical Methods has methods based on gas chromatography which are suitable for common aromatic and aliphatic amines as well as ethanolamines (67). Aromatic amines which diazotize readily can also be detected photometrically using a treated paper which changes color (68). Other methods based on infrared spectroscopy (69) and mass spectroscopy (70) have also been reported.

Handling of Amines. Regulations governing the safe handling and shipping of amines in interstate commerce are given in U.S. Department of Transportation publications (71). Specific information on the safe handling and hazards associated with a particular amine can be found in the Material Safety Data Sheet for that material. For further information on the safety of industrial material see also references 72 and 73.

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AMINOACETIC ACID, $\text{NH}_2\text{CH}_2\text{COOH}$.

See AMINO ACIDS (Glycine).

AMINO ACIDS

Survey,
L-Monosodium glutamate (MSG),

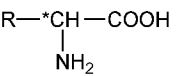
SURVEY

Amino acids are the main components of proteins. Approximately twenty amino acids are common constituents of proteins (1) and are called protein amino acids, or primary protein amino acids because they are found in proteins as they emerge from the ribosome in the translation process of protein synthesis (2), or natural amino acids. In 1820 the simplest amino acid, glycine, was isolated from gelatin (3); the most recently isolated, of nutritional importance, is L-threonine which was found (4) in 1935 to be a growth factor of rats. The history of the discoveries of the amino acids has been reviewed (5,6).

Hydroxylated amino acids (eg, 4-hydroxyproline, 5-hydroxylysine) and N-methylated amino acids (eg, N-methylhistidine) are obtained by the acid hydrolysis of proteins. γ-Carboxyglutamic acid occurs as a component of some sections of protein molecules; it decarboxylates spontaneously to L-glutamate at low pH. These examples are formed upon the nontranslational modification of protein and are often called secondary protein amino acids (1,6).

The presence of many nonprotein amino acids has been reported in various living metabolites, such as in antibiotics, some other microbial products, and in nonproteinaceous substances of animals and plants (7). Plant amino acids (8) and seleno amino acids (9) have been reviewed.

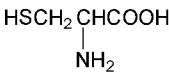
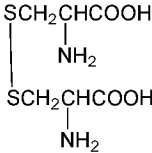
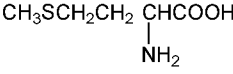
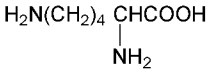
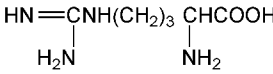
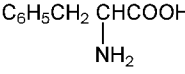
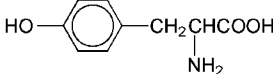
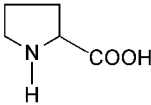
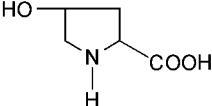
The general formula of an α-amino acid may be written:

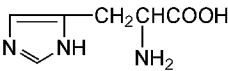
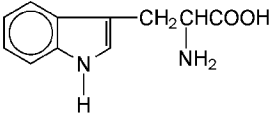
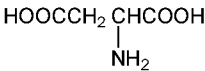
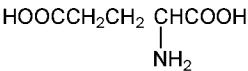
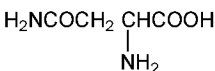
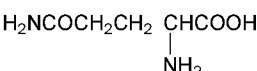


The asterisk signifies an asymmetric carbon. All of the amino acids, except glycine, have two optically active isomers designated D- or L-. Isoleucine and threonine also have centers of asymmetry at their β-carbon atoms (1,10). Protein amino acids are of the L-α-form (1,10) as illustrated in Table 1.

Table 1. α-Amino Acids

Common name	CAS Registry Number	Abbreviati on	Systematic name	Formula	Molecular weight
<i>Monocarboxylic</i>					
<i>Aliphatic</i>					
glycine	[56-40-6]	Gly	aminoacetic acid	H ₂ NCH ₂ COOH	75.07
alanine	[6898-94-8 /]	Ala	2-amino-propanoic acid	$\begin{array}{c} \text{CH}_3\text{CHCOOH} \\ \\ \text{NH}_2 \end{array}$	89.09
L-alanine	[56-41-7]	Val	2-amino-3-methyl-but anoic acid	$\begin{array}{c} (\text{CH}_3)_2\text{CH CHCOOH} \\ \\ \text{NH}_2 \end{array}$	117.15
D-alanine	[338-69-2]				
DL-alanine	[302-72-7]				
valine ^a	[7004-03-7 /]				
L-valine	[72-18-4]	Leu	2-amino-4-methyl-pen tanoic acid	$\begin{array}{c} (\text{CH}_3)_2\text{CHCH}_2 \text{CHCOOH} \\ \\ \text{NH}_2 \end{array}$	131.17
D-valine	[640-68-6]				
DL-valine	[516-06-3]				
leucine ^a	[7005-03-0 /]				
L-leucine	[61-90-5]	Ileu	2-amino-3-methyl-pen tanoic acid	$\begin{array}{c} \text{CH}_3\text{CH}_2 \text{CH}-\text{CHCOOH} \\ \quad \\ \text{CH}_3 \text{NH}_2 \end{array}$	131.17
D-leucine	[328-38-1]				
DL-leucine	[328-39-2]				
isoleucine ^a	[7004-09-3 /]				
L-isoleucine	[73-32-5]	Ser	2-amino-3-hydroxy-pr opanoic acid	$\begin{array}{c} \text{HOCH}_2 \text{CHCOOH} \\ \\ \text{NH}_2 \end{array}$	105.09
D-isoleucine	[319-78-8]				
DL-isoleucine	[443-79-8]				
<i>Aliphatic containing</i> —OH, —S—, —NH— group serine	[6898-95-9 /]				
L-serine	[56-45-1]	Thr	2-amino-3-hydroxy-bu tanoic acid	$\begin{array}{c} \text{CH}_3\text{CH}-\text{CHCOOH} \\ \quad \\ \text{OH} \text{NH}_2 \end{array}$	119.12
D-serine	[312-84-5]				
DL-serine	[302-84-1]				
threonine ^a	[36676-50-3 /]				

L-threonine D-threonine DL-threonine cysteine	[72-19-5] [632-20-2] [80-68-2] [4371-52-2 /	Cys	2-amino-3-mercapto- propanoic acid		121.16
L-cysteine D-cysteine DL-cysteine cystine	[52-90-4] [921-01-7] [3374-22-9 /] [24645-67-8]	(Cys) ₂	3,3'-dithio-bis-(2-amin o-propanoic acid)		240.30
L-cystine D-cystine DL-cystine methionine ^a	[56-893] [349-46-2] [923-32-0] [7005-18-7 /	Met	2-amino-4-methyl-thi obutanoic acid		149.21
L-methionine D-methionine DL-methionine lysine ^a	[63-68-3] [348-67-4] [59-51-8] [6899-06-5 /	Lys	2,6-diamino-hexanoic acid		146.19
L-lysine D-lysine DL-lysine arginine ^b	[56-87-1] [923-27-3] [70-54-2] [7004-12-8 /	Arg	2-amino-5-guani-dope ntanoic acid		174.20
L-arginine D-arginine DL-arginine <i>Aromatic</i> phenylalanine ^a	[74-79-3] [157-06-2] [7200-25-1 /] [3617-44-5 /	Phe	2-amino-3-phenyl-pro panoic acid		165.19
L-phenylalanine D-phenylalanine DL-phenylalanine tyrosine	[63-91-2] [673-06-3] [150-30-1] [55520-40-6]	Tyr	2-amino-3-(4-hydroxy -phenyl)-propanoic acid		181.19
L-tyrosine D-tyrosine DL-tyrosine <i>Heterocyclic</i> proline	[60-18-4] [556-02-5] [556-03-6] [7005-20-1 /	Pro	2-pyrrolidine-carboxyli c acid		115.13
L-proline D-proline DL-proline hydroxyproline	[147-85-3] [344-25-2] [609-36-9] (cis)	Hypro	4-hydroxy-2-pyrrolidin e-carboxylic acid		131.13
L-hydroxyproline D-hydroxyproline	[618-27-9] [2584-71-6 /				

DL-hydroxyproline	[49761-17-3]				
hydroxyproline	(trans)				
L-hydroxyproline (trans)	[51-35-4]				
D-hydroxyproline (trans)	[3398-22-9]				
	/				
DL-hydroxyproline (trans)	[618-28-0]				
histidine ^b	[7006-35-1]	His	2-amino-3-imidazole-propanoic acid		155.16
	/				
L-histidine	[71-00-1]				
D-histidine	[351-50-8]				
DL-histidine	[4998-57-6]				
	/				
tryptophan ^a	[6912-86-3]	Trp	2-amino-3-indoyl-propanoic acid		204.22
	/				
L-tryptophan	[73-22-3]				
D-tryptophan	[153-94-6]				
DL-tryptophan	[54-12-6]				
	/				
aspartic acid	[6899-03-2]	Asp	<i>Dicarboxylic</i> 2-amino-butane-dioic acid		133.10
	/				
L-aspartic acid	[56-84-8]				
D-aspartic acid	[1783-96-6]				
	/				
DL-aspartic acid	[617-45-8]				
glutamic acid	[6899-05-4]	Glu	2-amino-pentane-dioic acid		147.13
	/				
L-glutamic acid	[56-86-0]				
D-glutamic acid	[6893-26-1]				
	/				
DL-glutamic acid	[617-65-2]				
asparagine	[7006-34-0]	Asn	2-amino-3-carbamoyl-propanoic acid		132.12
	/				
L-asparagine	[70-47-3]				
D-asparagine	[2058-58-4]				
	/				
DL-asparagine	[3130-87-8]				
	/				
glutamine	[6899-04-3]	Gln	2-amino-4-carbamoyl-butanoic acid		146.15
	/				
L-glutamine	[56-85-9]				
D-glutamine	[5959-95-5]				
	/				
DL-glutamine	[585-21-7]				

^a Essential amino acid.

^b Arginine and histidine are also essential for children (6).

Amino acids are important components of the elementary nutrients of living organisms. For humans, ten amino acids are essential for existence and must be ingested in food. The nutritional value of proteins is governed by the quantitative and qualitative balance of individual essential amino acids.

The nutritional value of a protein can be improved by the addition of amino acids of low abundance in that protein. Thus the fortification of plant proteins such as wheat, corn, and soybean with L-lysine, DL-methionine, or other essential amino acids (L-tryptophan and L-threonine) is expected to alleviate some food problems (11). Such fortification has been widespread in the feedstuff of domestic animals.

Proteins are metabolized continuously by all living organisms, and are in dynamic equilibrium in living cells (6,12). The role of amino acids in protein biosynthesis has been described (2). Most of the amino acids absorbed through the digestion of proteins are used to replace body proteins. The remaining portion is metabolized into various bioactive substances such as hormones and purine and pyrimidine nucleotides, (the precursors of DNA and RNA) or is consumed as an energy source (6,13).

The history of the discovery of amino acids is closely related to advances in analytical methods. Initially, quantitative and qualitative analysis depended exclusively upon crystallization from protein hydrolysates. The quantitative precipitation of several basic amino acids including phosphotungstates, the separation of amino acid esters by vacuum distillation, and precipitation by sulfonic acid derivatives were developed successively during the last century.

After World War II, analytical methods for amino acids were improved and new methods were introduced. The first was microbial assay using lactic acid bacteria which require all of the regular amino acids for growth. Manometric determination (by use of a Warburg manometer) of CO₂ liberated by the

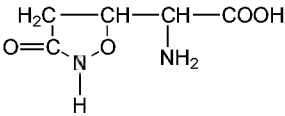
action of amino acid decarboxylase is now also classical. However, these methods are still used for the microdetermination of amino acids. Later, chromatographic separations using filter paper, ion-exchange resins, and other adsorbants were rapidly developed. Automatic analyzers of amino acids using ion-exchange resin chromatography (14) are now used widely in routine analyses of amino acid mixtures. More recently, high performance liquid chromatography (hplc) has been extensively developed and the separate determination of L- and D-amino acids has been possible by this method. Amino acid sensors have been studied (15,16). The contribution of various biosynthetic pathways for amino acids has been analyzed by ¹³C-nmr with glucose, labeled with carbon-13 at C-1 or C-6, as substrate (17).

The determination of amino acids in proteins requires pretreatment by either acid or alkaline hydrolysis. However, L-tryptophan is decomposed by acid, and the racemization of several amino acids takes place during alkaline hydrolysis. Moreover, it is very difficult to confirm the presence of cysteine in either case. The use of methanesulfonic acid (18) and mercaptoethanesulfonic acid (19) as the protein hydrolyzing reagent to prevent decomposition of L-tryptophan and L-cysteine is recommended. Enzymatic hydrolysis of proteins has been studied (20).

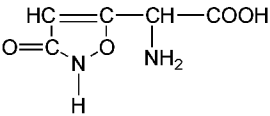
In 1950 all L-amino acids were manufactured by isolation from protein hydrolyzates or by separation of L-amino acids from the synthesized racemic mixtures. Since the mid-1950s, methods of production of L-amino acids have changed extensively. The first important change was made by the invention of a new fermentation process using so-called glutamic acid bacteria (eg, *Corynebacterium glutamicum*, *Brevibacterium flavum*) to produce L-glutamic acid (21). Thereafter, fermentation processes were developed to produce many other amino acids. Most amino acids (except for glycine, L-methionine, L-cysteine, and L-serine) are now economically produced by fermentation (22,23). Subsequently, enzymatic processes were developed to produce L-aspartic acid, L-alanine, L-tryptophan, L-cysteine, L-serine, L-lysine, L-phenylalanine, and some D-amino acids from chemically synthesized substrates (24). Glycine, DL-alanine, DL-methionine, and DL-cysteine, and some other amino acids are still produced by chemical synthesis. Chemical manufacturing procedures for amino acids have been discussed (25).

All of the protein amino acids are currently available commercially and their uses are growing. Amino acids and their analogues have their own characteristic effects in flavoring, nutrition, and pharmacology.

In the food industries a number of amino acids have been widely used as flavor enhancers and flavor modifiers (see FLAVORS AND SPICES). For example, monosodium L-glutamate is well-known as a meat flavor-enhancer and an enormous quantity of it is now used in various food applications (see AMINO ACIDS, L MONOSODIUM GLUTAMATE (MSG)). Protein, hydrolyzed by acid or enzyme to be palatable, has been used for a long time in flavoring agents. The addition of L-glutamate, L-aspartate, glycine, DL-alanine, and other palatable amino acids can improve flavoring by these protein hydrolyzates. In addition, some nucleotides, such as 5'-inosinic acid [131-99-7] and 5'-guanylic acid [85-32-5], have a synergistic effect on the meat flavor enhancing effects of L-glutamate and L-aspartate. Tricholomic acid [2644-49-7] (1) and ibotenic acid [2552-55-8] (2), nonprotein amino acids found in mushrooms, have 4 to 25 times stronger umami taste than L-glutamic acid (26). However, they have not been used in food. (See Table 13 and surrounding text for a definition of umami).



(1)



(2)

Some peptides have special tastes. L-Aspartyl phenylalanine methyl ester is very sweet and is used as an artificial sweetener (see SWEETENERS). In contrast, some oligopeptides (such as L-ornithinylnaurine ·HCl and L-ornithinyl-β-alanine ·HCl), and glycine methyl or ethyl ester ·HCl have been found to have a very salty taste (27).

Amino acids are also used in medicine. Amino acid infusions prepared from crystalline amino acids are used as nutritional supplements for patients before and after surgery. Some amino acids and their analogues are used for treatment of major diseases. L-DOPA, L-3-(3,4-dihydroxyphenyl)alanine, [59-92-7] is an important drug in the treatment of Parkinson's disease, and L-glutamine and its derivatives are used for treatment of stomach ulcers. α-Methyl-DOPA [555-30-6] is an effective antidepressant (see PSYCHOPHARMACOLOGICAL AGENTS). Some peptides, eg, oxytocin [50-56-6], angiotensin [1407-47-2], gastrin, and cerulein, have hormonal effects which have medical utility. The physiological effect of glutathione [70-18-8] (L-glutamyl-L-cysteinyl glycine) has been reviewed (28).

Amino acid polymers like poly(γ-methyl-L-glutamate) [29967-97-3] have been developed as raw materials for artificial leathers (see LEATHERLIKE MATERIALS). Derivatives of amino acids are now finding new applications in industry and agriculture.

Physical Properties

Melting Point. Amino acids are solids, even the lower carbon-number amino acids such as glycine and alanine. The melting points of amino acids generally lie between 200 and 300°C. Frequently amino acids decompose before reaching their melting points (Table 2).

Table 2. Physical Constants of Amino Acids^a

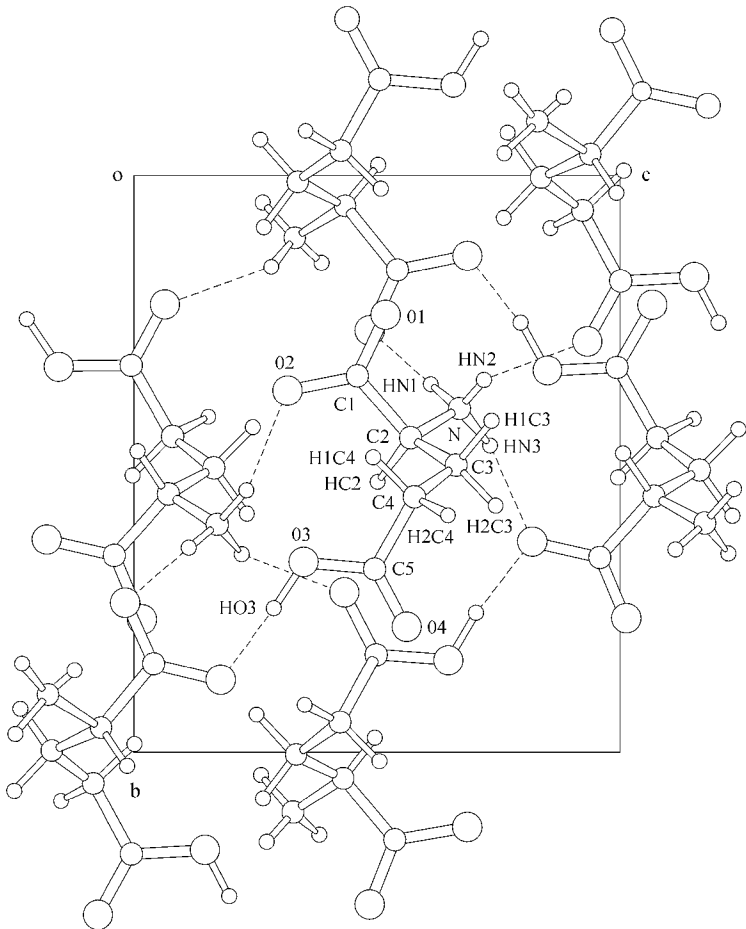
Amino acid		Melting point, °C	Density, d _{t1} ²	Specific rotation			Solvent
				[α] _D	t, °C	c, °	
Ala	L-	297 (dec)	1.401	+2.8	25	6	H ₂ O
		314 (dec)	1.432 ²³	+2.8	25	6	H ₂ O
	L·HCl	204 (dec)		+8.5	26	9.3	
	D-	314 (dec)		13.6	25	1	6 N HCl
	DL-	264 (dec)	1.424				
Arg		295 (dec)	1.424				
	L-	244 (dec)		+12.5	20	3.5	H ₂ O
	L·HCl	235 (dec)		+12.0	20	4	
Asn		DL-					
		217–218					
	L·H ₂ O	234–235	1.543 ¹⁵ ₄	5.42	20	1.3	
	D·H ₂ O	215		+5.41	20	1.3	
		234.5	1.543 ¹⁵ ₄	+5.41	20	1.3	

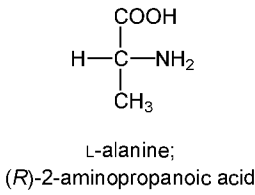
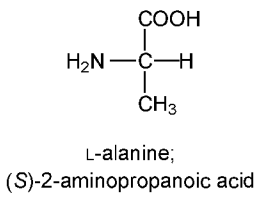
Asp	DL- ·H ₂ O	182–183	1.4540 ¹⁵ ₄				
	L-	270–271	1.661 ¹² ₅	†25.0	20	1.97	6 N HCl
		324 (dec)	1.6613 ¹³ ₁₃	†24.6	24	2	6 N HCl
	D-			23.0	27	2.30	6 N HCl
		269–271	1.6613 ¹³ ₁₃	25.5	20		HCl
	DL-	338–339	1.6632 ¹³ ₁₃				
Cys	L-			†6.5	25		5 N HCl
		240 (dec)		†9.8	30	1.3	H ₂ O
(Cys) ₂	L- ·HCl	175–178		†5.0	25		5 N HCl
	L-	260–261 (dec)	1.677	223.4	20	1	1 N HCl
	D-			†223	20		1 N HCl
Glu		247–249		†224	20	1	1 N HCl
	DL-	260					
	L-	247–249 (dec)	1.538 ²⁰ ₄	†31.4	22.4		6 N HCl
		224–225 (dec)	1.538 ²⁰ ₄	†31.4	22	1	6 N HCl
	L- ·HCl	214 (dec)		†24.4	22	6	
Gly	D-			30.5	20	1.0	6 N HCl
		213 (dec)	1.538 ²⁰ ₄	31.7	25		1.7 N HCl
	DL-	225–227 (dec)	1.4601 ²⁰				
		199 (dec)	1.4601 ²⁰ ₄				
		233 (dec)	1.1607				
His		262 (dec)	0.828 ¹⁷				
	L-	287 (dec)		39.74	20	1.13	
		287 (dec)		39.7	20	1.13	H ₂ O
	L- ·HCl ·H ₂ O	259 (dec)		†8.0	26	2	3 N HCl
	D-	287 (dec)		†40.2	20		H ₂ O
	DL-	285 (dec)					
Ileu	L-	284 (dec)		†11.29	20	3	
				†40.61	20	4.6	6.1 N HCl
		285–286 (dec)		†12.2	25	3.2	H ₂ O
Leu				†36.7		4	1 N HCl
	D-	283–284 (dec)		12.2	20	3.2	H ₂ O
				40.7		1	5 N HCl
	DL-	280 (dec)					
	L-	293–295 (dec)		10.8	25	2.2	
Lys		293–295	1.293 ¹⁸ ₄	10.42	25	22	H ₂ O
	D-	293		†10.34	20		
	DL-	332 (dec)					
		293–295	1.293 ¹⁸ ₄				
	L-	224.5 (dec)		†25.9	23	2	6 N HCl
Met		224–245 (dec)		†14.6	20	6	H ₂ O
	L- ·HCl	263–264		†14.6	25	2	0.6 N HCl
	L- ·2HCl	193		†15.3	20	2	
		201–202		†15.29	20		H ₂ O
	DL- ·HCl	260–263					
Phe	DL- ·2 HCl	187–189					
	L-	280–282 (dec)		8.2	25		
		283 (dec)		8.2	25	1	H ₂ O
Pro	DL-	281 (dec)	1.340				
	L-	283 (dec)		35.1	20	1.94	
	D-	285 (dec)		†35.0	20	2.04	
Ser	DL-	271–273 (dec)					
	L-	220–222 (dec)		52.6	20	0.58	0.5 N HCl
		220–222 (dec)		80.9	20	1	H ₂ O
Thr	DL-	205 (dec)					
	L-	274		76.5		2.5	H ₂ O
		228 (dec)		6.83	20	10	H ₂ O
Tyr	D-	228 (dec)		†6.87	20	10	H ₂ O
	DL-	246 (dec)	1.537				
		246 (dec)	1.603 ²² ₅				
Val	L-	255–257 (dec)		28.3	26	1.1	
	DL-	229–230 (dec)					
	L-	289 (dec)		31.5	23	1	
Trp				†2.4	20		0.5 N HCl
				†0.15	20	2.43	0.5 N NaOH
		290–292 (dec)		31.5	20	0.5	H ₂ O
				†6.1	20	11	1 N NaOH
	D-	281–282		†33	20		H ₂ O
Tyr	DL-	282					
	L-	342–344 (dec)	1.456	10.6	22	4	1 N HCl
				13.2	18	4	3 N NaOH
Val	D-	310–314 (dec)		†10.3	25	4	1 N HCl
	DL-	316 (dec)					
		340 (dec)					
Val	L-	315	1.230	†22.9	23	0.8	20 ⁰ ° HCl

	93–96(?)	1.230	$\mp$ 22.9	23	0.8	20° o alc
D-	156–157.5		29.4	20		20° o alc
DL-	298 (dec)	1.310				

^a From refs. 29 and 30.

Crystalline Structures. Crystal shape of amino acids varies widely, for example, monoclinic prisms in glycine and orthorhombic needles in L-alanine. X-ray crystallographic analyses of 23 amino acids have been described (31). L-Glutamic acid crystallizes in two polymorphic forms (α and β) (32), and the α -form is more facily handled in industrial processes. The crystal structure has been determined (33) and is shown in Figure 1.





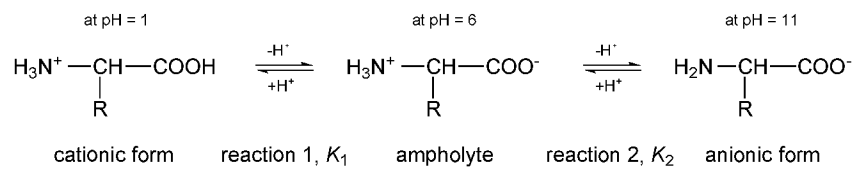
Solubility. Solubility data of amino acids are given in Table 3. In all instances there are at least two polar groups, acting synergistically on the solubility in water. The solubility of amino acids having additional polar groups, eg, $-\text{OH}$, $-\text{SH}$, $-\text{COOH}$, $-\text{NH}_2$, is even more enhanced.

Table 3. pK and pI at 25 °C and Solubility of Amino Acids^a

Amino acid		pK_1 (COOH)	pK_2 (NH ₃ ⁺) ^b	pK_3 (NH ₃ ⁺)	pI	Solubility in water, g/L				
						0°C	25°C	50°C	75°C	100°C
<i>Divalent acids</i>										
Gly		2.34	9.60		5.97		250	391	544	672
Ala	L-	2.34	9.69 ^c		6.00	127.3	166.5	217.9	285.1	373.0
	DL	2.35	9.87			121	167	231	319	440
	-									
Val	L-	2.32	9.62 ^c		5.96	83.4	88.5	96.2	102.4 (65°C)	
	DL	2.29	9.72			59.8	70.9	91.1	126.1	188.1
	-									
Leu	L-				5.98	22.7	24.26	28.87	38.23	56.38
	DL	2.36	9.60			7.97	9.91	14.06	22.76	42.06
	-									
Ileu	L-	2.26	9.62 ^c		5.94	37.9	41.2	48.2	60.8	82.6
	DL	2.32	9.76			18.3	22.3	30.3	46.1	78.0
	-									
Ser	L-	2.21	9.15 ^c		5.68			soluble		
	DL	2.21	9.15			22.04	50.23	103	192	322
	-									
Thr	L-	2.15	9.12		5.64			freely soluble		
Pro	L-	1.99	10.60		6.30	1272	1623	2067	2509 (70°C)	
Hyp	L-	1.82	9.65		5.74	288.6	361.1	451.8	516.7 (65°C)	
Phe	L-	1.83	9.13 ^c		5.48	19.8	29.6	44.3	66.2	99.0
	DL	2.58	9.24			9.97	14.11	21.87	37.08	68.9
	-									
Trp	L-	2.38	9.39		5.89	0.23	11.4	17.1	27.95	49.9
Met	DL	2.28	9.21		5.74	18.18	33.81	60.70	105.2	176.0
	-									
<i>Trivalent acids</i>										
Asp	L-	1.88	3.65 (COOH)	9.60	2.77	2.1	5.0	12.0	28.8	68.9
Glu	L-	2.19	4.25 (COOH)	9.67	3.22		8.64	21.86	55.32	140.0
	DL						20.54	49.34	118.6	284.9
	-									
Tyr	L-	2.20	9.11	10.07 (OH)	5.66	0.196	0.453	1.052	2.438	5.65
	DL					0.147	0.351	0.836		
	-									
Cys	L-	1.71	8.33	10.78				freely soluble		
His	L-	1.78	5.97	8.97	7.47		41.9			
Arg	L-	2.18	9.09	13.2	11.1			the satd aq soln contains 15% (w/w) at 21°C		
					5					
Lys	L-	2.20	8.90	10.28 (38°C)	9.59			freely soluble		
<i>Tetravalent acids</i>										
Cys)	L-	<1	2.1 (COOH)	8.02 ^d	5.03	0.05	0.112	0.239	0.523	1.142

Refs. 29 and 35.
Unless indicated (COOH).
Ref. 36.
 pK_4 (NH_3^+) 8.71).

Dissociation. In aqueous solution, amino acids undergo a pH-dependent dissociation (37):



where

$$K_1 = \frac{[\text{H}^+][\text{H}_3\text{N}^+\text{CH(R)COO}^-]}{[\text{H}_3\text{N}^+\text{CH(R)COOH}]}$$
$$K_2 = \frac{[\text{H}^+][\text{H}_2\text{NCH(R)COO}^-]}{[\text{H}_3\text{N}^+\text{CH(R)COO}^-]}$$

These are the definitions of the two characteristic dissociation constants normally expressed in terms of pK . When three dissociating groups are present in a molecule there are three pK values, ie, pK_1 , pK_2 , pK_3 . A knowledge of these pK values is important in the separation or isolation of each amino acid by ion-exchange chromatography.

A large part of the dissolved amino acid exists as the ampholyte (zwitterion). The isoelectric point (pI) is the pH at which the net electric charge of a dissolved amino acid molecule is zero. pI is expressed as

$$pI = \frac{pK_1 + pK_2}{2}$$

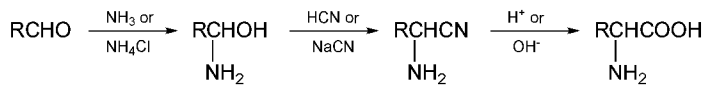
The solubility of each amino acid is minimal at its pI . pK and pI values are given in Table 3.

Chemical Properties

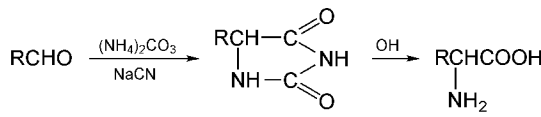
SYNTHESIS OF α -AMINO ACIDS

Many methods for chemical synthesis of α -amino acids have been established. Because excellent reviews have been published (25,38), well-known reactions are introduced here only by their names and synthetic pathways.

Strecker Synthesis



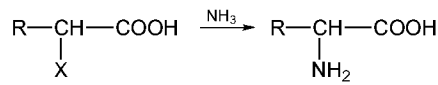
Bucherer Synthesis



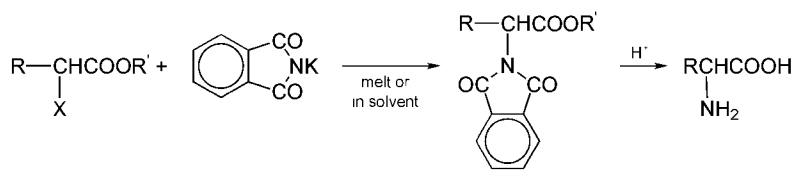
These two methods are popular for α -amino acid synthesis, and used in the industrial production of some amino acids since raw materials are readily available.

Amination of α -Halogeno Carboxylic Acids.

Original Method

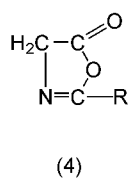
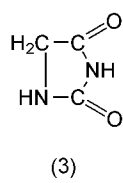


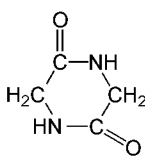
Gabriel's Modification



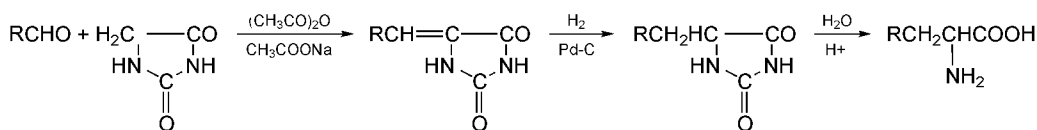
Alkylation of Active Methylene Compounds.

Erlenmeyer Synthesis and Others. Hydantoin [461-72-3] (3), azlactone (4), diketopiperazine [106-57-0] (5), etc, are readily available, so that these methods are often utilized. In structure (4), $\text{R} = \text{CH}_3$ [24474-93-9] or $\text{R} = \text{C}_6\text{H}_5$ [1199-01-5].

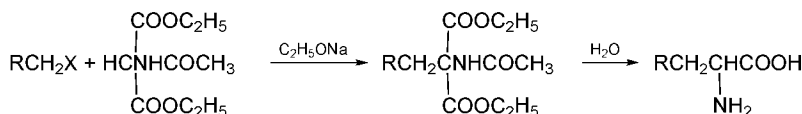




(5)

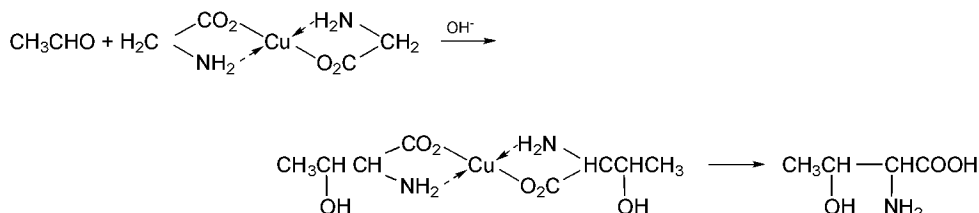


Reaction with Alkyl Halide. The active methylene group of an *N*-acylamino-malonic acid ester or *N*-acylamino cyanoacetic acid ester condenses readily with primary alkyl halides.

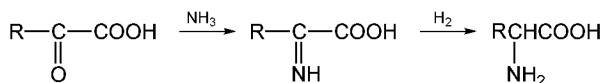


Also, Michael addition reactions occur between *N*-acylaminomalonic acid esters and unsaturated compounds, ie, acrolein [107-02-8], acrylonitrile [107-13-1], acrylic acid esters, and amino acids result from hydrolysis of the addition products.

Reaction of Bisglycinatocopper(II). Bisglycinatocopper(II) [13479-54-4] condenses with aliphatic aldehydes. Removal of copper from the condensate results in β-hydroxy-α-amino acid. This is a classical synthetic method of DL-threonine, but the formation of *allo*-isomer is unavoidable.

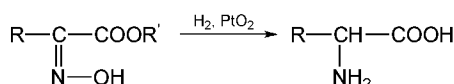


Amination of α-Keto Acids. α-Keto acids are catalytically reduced

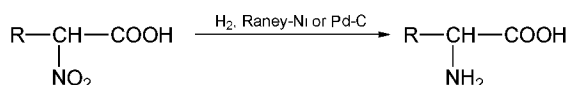


in the presence of ammonia. α-Keto acids are readily prepared by hydrolysis of substituted hydantoin or double carbonylation of benzyl halide in the case of phenylpyruvic acid [156-06-9]. Enzymatic amination of α-keto acids has been developed by many research groups (39).

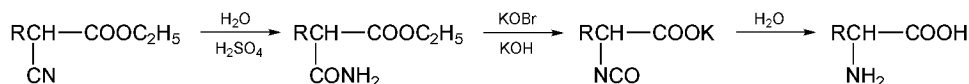
Reduction of α-Ketoxime



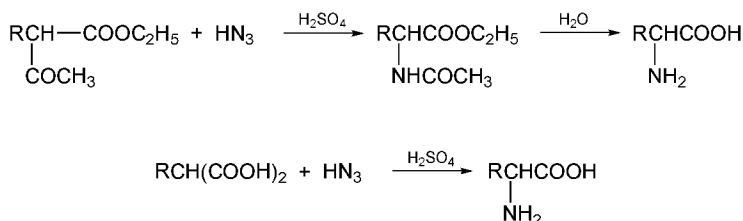
Reduction of α-Nitro Carboxylic Acid



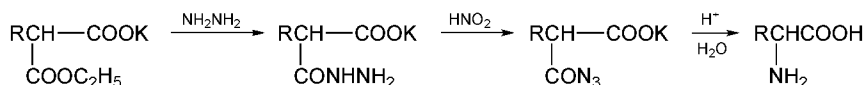
Hofmann Degradation

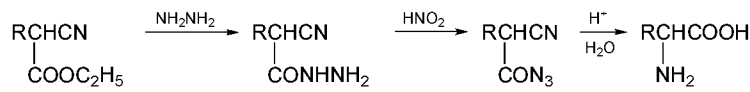


Schmidt Reaction

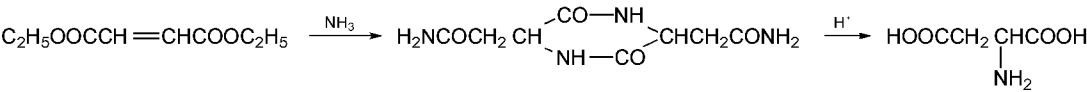


Curtius Degradation

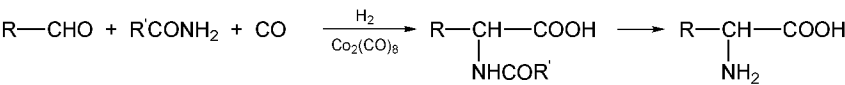




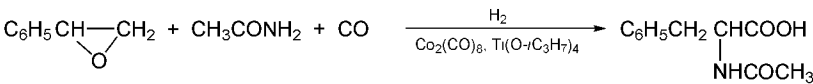
Amine Addition to Double Bond. Production of D,L-aspartic acid from maleic acid ester or fumaric acid ester is a typical example.



Carbonylation of Aldehyde. This method (40,41) is noteworthy as an efficient one-step synthesis.
Wakamatsu Reaction



Modified Method

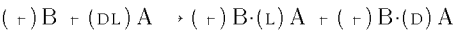


OPTICAL RESOLUTION

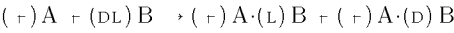
In many cases only the racemic mixtures of α-amino acids can be obtained through chemical synthesis. Therefore, optical resolution (42) is indispensable to get the optically active L- or D-forms in the production of expensive or uncommon amino acids. The optical resolution of amino acids can be done in two general ways: physical or chemical methods which apply the stereospecific properties of amino acids, and biological or enzymatic methods which are based on the characteristic behavior of amino acids in living cells in the presence of enzymes.

Crystallization Method. Such methods as mechanical separation, preferential crystallization, and substitution crystallization procedures are included in this category. The preferential crystallization method is the most popular. The general procedure is to inoculate a saturated solution of the racemic mixture with a seed of the desired enantiomer. Resolutions by this method have been reported for histidine (43), glutamic acid (44), DOPA (45), threonine (46), N-acetyl phenylalanine (47), and others. In the case of glutamic acid, the method had been used for industrial manufacture (48).

Diastereoisomeric Salts. The formation of salts of optically active bases with racemic acids or of optically active acids with racemic bases leads to diastereomeric mixtures which may be resolved by the differential solubility of the components of such mixtures (49), ie,



or



The salts in turn may be decomposed by a metathetical reaction involving a stronger base than (+)B or stronger acid than (+)A.

Typical examples of optically active materials for resolution are as follows:

Name	Configuration	CAS Registry Number
<i>Acidic</i>		
camphorsulfonic acid	D	[3144-16-9]
camphoric acid	R	[124-83-4]
camphoric acid	S	[560-09-8]
tartaric acid	D	[147-71-7]
tartaric acid	L	[87-69-4]
dibenzoyltartaric acid	R	[2743-38-6]
dibenzoyltartaric acid	S	[17026-42-5]
malic acid	R	[636-61-3]
malic acid	S	[97-67-6]
mandelic acid	R	[611-71-2]
mandelic acid	S	[17199-29-0]
glutamic acid	L	[56-86-0]
<i>Basic</i>		
brucine		[357-57-3]
cinchonidine	R	[485-71-2]
ephedrine	R	[299-42-3]
strychnine		[57-24-9]
morphine		[52-27-2]
α-methylbenzylamine	R	[3886-69-9]
α-methylbenzylamine	S	[2627-86-3]
1-(1-naphthyl)ethylamine	R	[3886-70-2]
1-(1-naphthyl)ethylamine	S	[10420-89-0]
1-phenyl-2-(p-toly)ethylamine	R	[30339-32-3]
1-phenyl-2-(p-toly)ethylamine	S	[30339-30-1]

This procedure is restricted mainly to aminodicarboxylic acids or diaminocarboxylic acids. In the case of neutral amino acids, the amino group or carboxyl group must be protected, eg, by N-acylation, esterification, or amidation. This protection of the racemic amino acid and deprotection of the separated enantiomers add stages to the overall process. Furthermore, this procedure requires a stoichiometric quantity of the resolving agent , which is then difficult to recover efficiently. Practical examples of resolution by this method have been published (50,51).

Enzymatic Method. L-Amino acids can be produced by the enzymatic hydrolysis of chemically synthesized DL-amino acids or derivatives such as esters, hydantoins, carbamates, amides, and acylates (24). The enzyme which hydrolyzes the L-isomer specifically has been found in microbial sources. The resulting L-amino acid is isolated through routine chemical or physical processes. The D-isomer which remains unchanged is racemized chemically or enzymatically and the process is recycled. Conversely, enzymes which act specifically on D-isomers have been found. Thus various D-amino acids have been

produced (see Table 10).

In another procedure, D-amino acid oxidase (52) is useful to produce L-amino acids from DL-amino acids. α-Ketocarboxylic acids which are formed by the action of enzymes on D-amino acids, are aminated to form L-amino acids by coupling through the action of amino acid aminotransferases (53).

In these procedures, the choice of derivatives and enzyme is important. Sometimes it is possible to get a D-amino acid which remains in the microbial culture supplemented with DL-amino acids (54).

Chromatographic Method. Progress in the development of chromatographic techniques (55), especially, in high performance liquid chromatography, or hplc, is remarkable (56). Today, chiral separations are mainly carried out by three hplc methods: chiral hplc columns, achiral hplc columns together with chiral mobile phases, and derivatization with optical reagents and separation on achiral columns. All three methods are useful but none provides universal application.

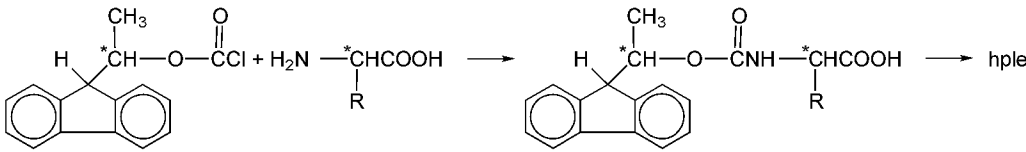
Chiral Hplc Columns. There are about 40 commercially available chiral columns which are suitable for analytical and preparative purposes (57). In spite of the large number of commercially available chiral stationary phases, it is difficult and time-consuming to obtain good chiral separation. In order to try a specific resolution meaningfully, a battery of chiral hplc columns is necessary and this is quite expensive.

Among various types of chiral stationary phases, the host-guest type of chiral crown ether is able to separate most amino acids completely (58).

Achiral Columns Together with Chiral Mobile Phases. Ligand-exchange chromatography for chiral separation has been introduced (59), and has been applied to the resolution of several α-amino acids. Prior derivatization is sometimes necessary. Preparative resolutions are possible, but the method is sensitive to small variations in the mobile phase and sometimes gives poor reproducibility.

The principle of this method depends on the formation of a reversible diastereomeric complex between amino acid enantiomers and chiral addends, by coordination to metal, hydrogen bonding, or ion–ion mutual action, in the presence of metal ion if necessary. L-Proline (60), L-phenylalanine (61), N-(p-toluene sulfonyl)-L-phenylalanine (62), L-histidine methyl ester (63), N-acetyl L-valine t-butyl amide (64), etc, are used as chiral addends.

Derivatization with Optically Active Reagents and Separation on Achiral Columns. This method has been reviewed (65); a great number of homochiral derivatizing agents (HDA) are described together with many applications. An important group is the chloroformate HDAs. The reaction of chloroformate HDAs with racemic, amino-containing compounds yields carbamates, which are easily separated on conventional hplc columns, eg (66),



Gas chromatography (gc) is inferior to hplc in separating ability. With gc, it is better to use capillary columns and the application is then limited to analysis (67). Resolution by thin layer chromatography or tlc is similar to lc, and chiral stationary phases developed for lc can be used. However, tlc has not been studied as extensively as lc and gc. Chiral plates for analysis and preparation of micro quantities have been developed (68).

A new technique referred to as the liquid membrane method has been developed (69). Immobilized liquid membranes are expected to become practical because of many advantages.

Enzymatic hydrolysis of N-acylamino acids by amino acylase and amino acid esters by lipase or carboxy esterase (70) is one kind of kinetic resolution. Kinetic resolution is found in chemical synthesis such as by epoxidation of racemic allyl alcohol and asymmetric hydrogenation (71). New routes for amino acid manufacturing are anticipated.

ASYMMETRIC SYNTHESIS

Asymmetric synthesis is a method for direct synthesis of optically active amino acids and finding efficient catalysts is a great target for researchers. Many excellent reviews have been published (72). Asymmetric syntheses are classified as either enantioselective or diastereoselective reactions. Asymmetric hydrogenation has been applied for practical manufacturing of L-DOPA and L-phenylalanine, but conventional methods have not been exceeded because of the short life of catalysts. An example of an enantioselective reaction, asymmetric hydrogenation of α-acetamidocinnamic acid derivatives, eg, Z-2-acetamidocinnamic acid [55065-02-6] (6), is shown below and in Table 4 (73).

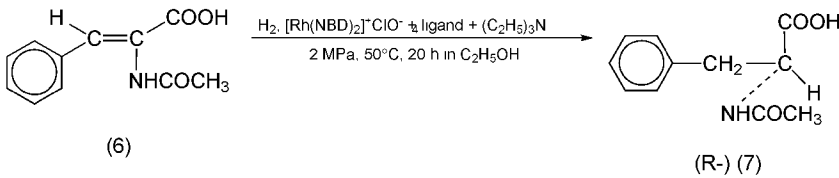
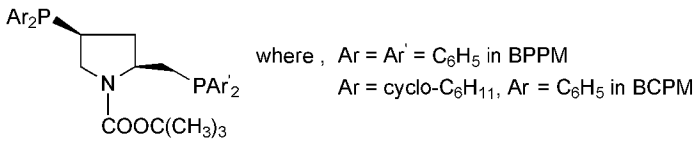


Table 4. Asymmetric Hydrogenation of (Z)-2-Acetamidocinnamic Acid (6) to (R)-N-Acetylphenylalanine^a (7)

Ligand	Substrate [Rh]	Conversion, %	Enantiomeric excess, %
(2 <i>S</i> , 4 <i>S</i>)-BPPM	1000	100	78.0
	10000	11	79.7
(2 <i>S</i> , 4 <i>S</i>)-BCPM	10000	100	37.0
(2 <i>S</i> , 4 <i>S</i>)- <i>o</i> -methoxy-BPPM	1000	100	98.0
	10000	64	98.9
(2 <i>S</i> , 4 <i>S</i>)- <i>m</i> -methoxy-BPPM	1000	100	84.8
	10000	7	
(2 <i>S</i> , 4 <i>S</i>)- <i>p</i> -methoxy-BPPM	1000	100	90.4
	10000	100	89.8

^a The R enantiomer is D-N-acetylphenylalanine [10172-89-1].

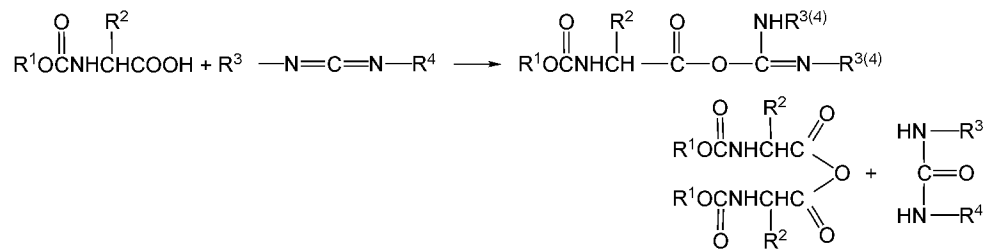
The ligands are phosphino derivatives of N-tert-butoxycarbonyl pyrrolidine, BPPM and BCPM:



Recent developments in asymmetric synthesis include asymmetric amplifying effects and the phenomenon of a nonlinear effect in which the

effective, but requires that the carboxyl group be esterified first (81). LiAlH_4 is inferior in terms of yield and practical convenience to $\text{LiAlH}_2(\text{OCH}_3)_2$ for the reduction of amino acid esters (82). Solvent effects have been reported in the case of LiAlH_4 (83).

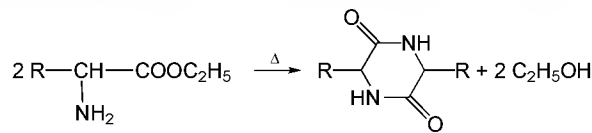
Anhydride Formation. The carboxyl group in *N*-protected amino acids is converted into the symmetrical anhydride on treatment with the carbodiimide (84).



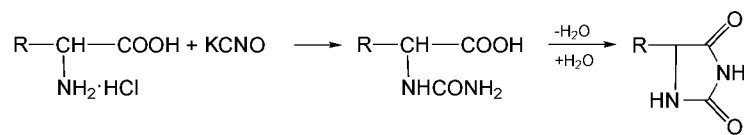
Cyclic anhydrides are formed readily from *N*-protected aspartic and glutamic acids.

Reactions Depending on Both Amino and Carboxyl Groups.

Formation of Diketopiperazines. Esters of α -amino acids can be readily prepared by refluxing anhydrous alcoholic suspensions of α -amino acids saturated with dry HCl. Diketopiperazines are formed by heating the alcoholic solution of the α -amino acid ester.



Formation of Hydantoin



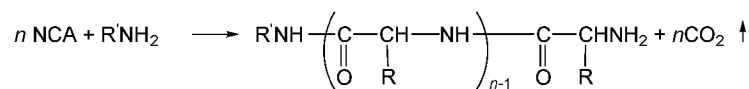
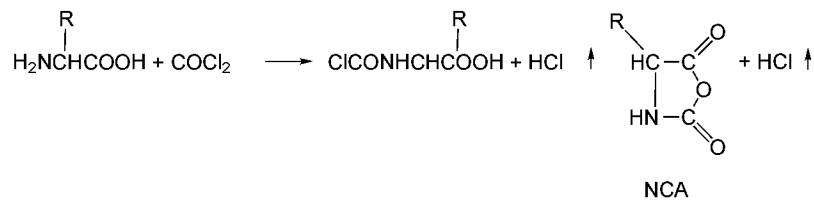
The use of an organic isocyanate instead of potassium isocyanate gives a *N*-substituted hydantoin.

Strecker Degradation (Oxidative Deamination). Mild oxidizing agents such as aqueous sodium hypochlorite or aqueous N-bromosuccinimide, cause decarboxylation and concurrent deamination of amino acids to give aldehydes.

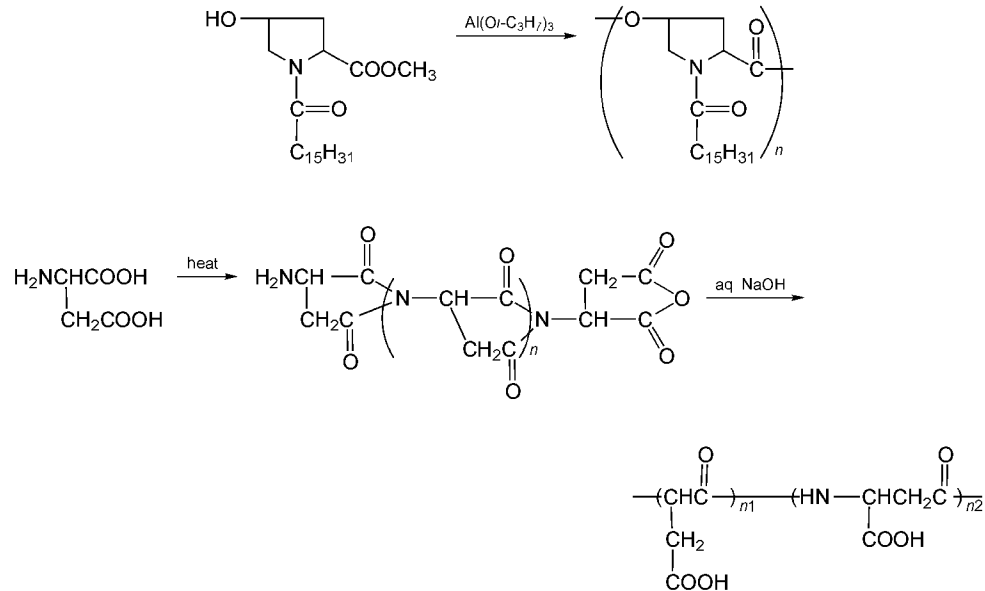


Similarly, silver(II) picolinate and lead tetraacetate can be used to produce carbonyl compounds.

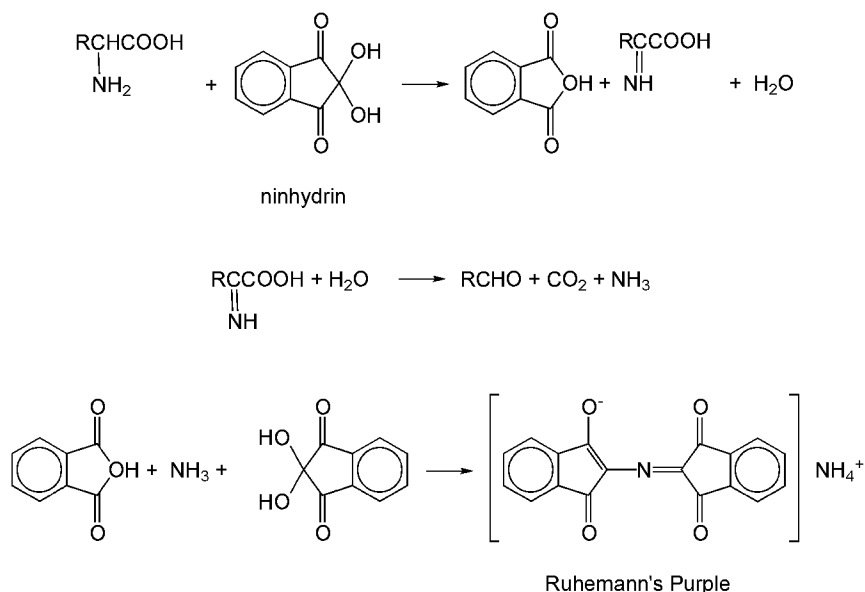
Formation of N-Carboxy- α -Amino Acid Anhydride (NCA) (85). NCAs are important as starting materials for amino acid polymers. They are prepared by the reaction of amino acids with phosgene in an aprotic solvent.



Although polymerization of NCA is popular, other types of amino acid polymerization have also been reported, for example (86,87):

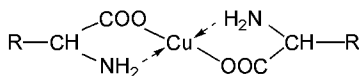


Ninhydrin-Color Reaction. This reaction is commonly used for qualitative analysis of α -amino acids, peptides, and proteins.



Other Reactions.

Salt Formation and Metal Chelation. Most α -amino acids form salts in alkaline and acidic aqueous solutions (88). For example, α -amino acids form inner complex salts with copper.



Benzenesulfonate compounds yield very insoluble salts which have been used for separation and identification of amino acids (89). Similarly, phosphotungstic acid forms insoluble salts with basic amino acids such as lysine, arginine, and cysteine.

Synthesis of Peptide. There is continual progress in the improvement of instruments and reagents for peptide synthesis, especially "solid phase polymerization" (90) (see PROTEINS). This method is suitable for the synthesis of peptides with 20 ~ 30 amino acid units.

Induction of Asymmetry by Amino Acids. No fewer than six types of reactions can be carried out with yields of 75–100% using amino acid catalysts, ie, catalytic hydrogenation, intramolecular aldol cyclizations, cyanhydrin synthesis, alkylation of carbonyl compounds, hydrosilylation, and epoxidations (91).

Biology of Amino Acids

Nutrition. Protein amino acids, which are not synthesized by the body and should be supplied as nutrients to maintain life, are called essential amino acids (6). For humans, L-arginine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-valine, L-threonine, and L-tryptophan are essential amino acids. However, in adults, L-arginine and L-histidine are somewhat synthesized in cells. For histidine, there is evidence that it is dietetically essential for the maintenance of nitrogen balance (92). On the other hand, those amino acids which are synthesized in apparently adequate amounts are nonessential amino acids: L-alanine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamic acid, L-glutamine, glycine, L-proline, L-serine, and L-tyrosine. Of these, L-tyrosine and L-cysteine are essential for children. Recent advances in nutritional studies of amino acids have led to development of amino acid transfusion (93).

The nutritional value of a protein can be improved by the addition of amino acids which are short in the protein (11). The amino acid score has been used to evaluate the nutritive value of food proteins. The reference pattern or scoring pattern of essential amino acids presented by the Food and Agriculture Organization of the World Health Organization (FAO WHO) in 1973 (94) and by FAO WHO of the United Nations in 1985 (95) has been used to calculate the amino acid score. The proportion of each essential amino acid in a particular protein to that of the reference pattern is calculated and an essential amino acid that has a score of less than 100% is called the limiting amino acid of the protein. If there are two or more essential amino acids of this kind, they are called the first limiting amino acid, the second limiting amino acid, and so on in ascending order of their percentage. The amino acid scores and the limiting amino acids of many foods have been calculated (96). Almost all of the plant proteins have limiting amino acids. The nutritionally important cereal proteins are particularly deficient in L-lysine and are also low in L-threonine and L-tryptophan. The limiting amino acid in soybean meal is methionine. No animal proteins, except for those of shellfish, mollusks, and crustaceans, have limiting amino acids.

Before the reference pattern was established, it was usual to use the amino acid composition of egg protein as a standard. The ratio of the amount of limiting amino acid present in a protein to that in egg protein is the chemical score of that protein. For practical purposes, the chemical score and the amino acid score are quantitatively similar. Because these are based on the chemical analysis of protein, both ignore the biological availability of the essential amino acids. The biological value (BV, the ratio of nitrogen retained in the body to that absorbed), the Net Protein Utilization (NPU, the BV of the protein multiplied by the digestibility), and the Protein Efficiency Ratio (PER, the gain in weight per gram of dietary protein) are biological measures. For details of protein quality, see references 6 and 96.

Feeding standards, which have been instituted nationally, indicate the amount of the essential amino acids (together with other nutrients) for the rational breeding of domestic animals. The feeding standards of the National Research Council (NRC) of the United States and Agricultural Research Council (ARC) of the United Kingdom are well known (the former indicates the minimal amount and the latter shows the recommended amount). Japanese Feeding Standards have been instituted (97).

Amino acids essential for young rats (98) and fishes (99) have been reviewed. Rats preferably eat a diet with sufficient amounts of essential amino acids rather than one that is deficient (100). Each essential amino acid, consumed in self-selection, has been reviewed (101). A protein diet with an excess of essential amino acids has been described as a poor protein diet from investigations that showed remarkable growth inhibition and occurrence of fatty liver disease in rats (102). This is called amino acid imbalance (103).

Biosynthesis of Protein. The dynamic equilibrium of body protein was confirmed by animal experiments using ^{15}N -labeled amino acids in 1939 (104). The human body is maintained by a continuous equilibrium between the biosynthesis of proteins and their degradative metabolism where the nitrogen lost as urea (about 85% of total excreted nitrogen) and other nitrogen compounds is about 12 g/d under ordinary conditions. The details of protein biosynthesis in living cells have been described (2,6) (see also PROTEINS).

Toxicity of α -Amino Acid. LD₅₀ values of α -amino acids are listed in Table 5. L-Lysine and L-arginine are mutually antagonistic. The addition of an excess of one reduces the biological value of protein and only the addition of the other overcomes the effect. The other antagonism occurs between the branched-chain amino acids (L-isoleucine, L-leucine, and L-valine). Pellagra is caused by L-leucine inhibition of niacin formation from L-tryptophan. People living on low protein nutrition and with only a marginally adequate intake of L-tryptophan and niacin, eg, living on sorghum as a dietary staple, are at a risk of developing pellagra if they have an excess intake of L-leucine (6).

Table 5. Toxicity^a of Amino Acids

Amino acid	LD ₅₀ ^b	
	Oral	Intraperitoneal
L-Arg·HCl	12 g	
L-Cys	5580 mg	1620 mg
L-Cys·HCl		1250 mg ^c
L-(Cys) ₂	25 g	
L-His	7930 mg	
L-Ileu		6822 mg
L-Leu		5379 mg
D-Leu		6429 mg
L-Lys·HCl	10 g	4019 mg
L-Met	36 g	4328 mg
L-Phe		5287 mg
D-Phe		5452 mg
DL-Thr		3098 mg
L-Trp		1634 mg
D-Trp		4289 mg
L-Val		5390 mg
D-Val		6093

^a Rat, unless otherwise noted.

^b Ref. 105.

^c Mouse.

In the case of hyperphenylalaninaemia, which occurs in phenylketonuria because of a congenital absence of phenylalanine hydroxylase, the observed phenylalanine inhibition of protein synthesis may result from competition between L-phenylalanine and L-methionine for methionyl-tRNA. Patients suffering from maple syrup urine disease, an inborn lack of branched chain oxo acid decarboxylase, are mentally retarded unless the condition is treated early enough. It is possible that the high level of branched-chain amino acids inhibits uptake of L-tryptophan and L-tyrosine into the brain. Brain injury of mice within ten days after their birth was reported as a result of hypodermic injections of monosodium glutamate (MSG) (0.5–4 g/kg). However, the FDA concluded that MSG is a safe ingredient, because mice are born with underdeveloped brains regardless of MSG injections (106).

Furthermore, the Joint Expert Committee on Food Additives (107) (JECFA) of the WHO and FAO of the United Nations issued the evaluation of the safety, stating that on the basis of the available data, the total dietary intake of glutamates arising from their use at the levels necessary to achieve the desired technological effect and from their acceptable background in food does not, in the opinion of the committee, represent a hazard to health.

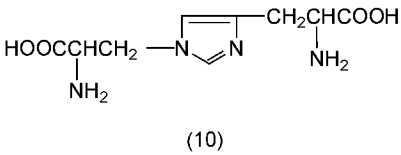
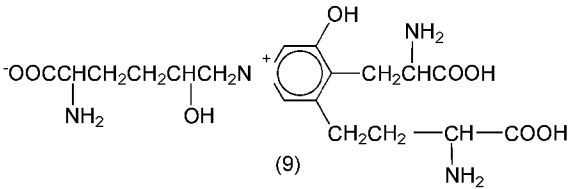
The nephrotoxic amino acid, lysinoalanine [18810-04-3], formed upon alkaline treatment of protein, was reported in 1964 (108). Its toxicity seems to be mitigated in protein in that it is not released by normal digestion (109). Naturally occurring new amino acids, which can be classified as proteinaceous or non-proteinaceous, can, as in the case of those from some legumes, show a remarkable toxicity (110). For the details of amino acid toxicity, see reference 6. Enzyme inhibition by amino acids and their derivatives have been reviewed (111).

Metabolism of Amino Acids. The amino acids are metabolized principally in the liver to a variety of physiologically important metabolites, eg, creatine (creatinine), purines, pyrimidines, hormones, lipids, amino sugars, urea, ammonia, carbon dioxide, and energy sources. The reactions of transamination, deamination, and decarboxylation are important for amino acid metabolism. Glutamate–oxalacetate transaminase (GOT) and glutamate–pyruvate transaminase (GPT) are the most important transaminases. NAD-dependent glutamic acid dehydrogenase, amino acid oxidases, and aspartic acid ammonia-lyase catalyze the deamination of amino acids. Amino acid decarboxylase is important to amine formation. The products of these enzyme reactions are metabolized finally to carbon dioxide and water via the pathways for sugar metabolism or fatty acid metabolism. The amino acids which are degraded via the former or the latter pathway are called glucogenic (or glycogenic) amino acids or ketogenic amino acids, respectively (13).

As Neurotransmitters. Several amino acids serve as specialized neurotransmitters in both vertebrate and invertebrate nervous systems. These amino acids can be classified as inhibitory transmitters, such as γ -aminobutyric acid [56-12-2] (GABA) and glycine, and excitatory amino acids, examples of which are L-glutamic acid and L-aspartic acid. A number of other amino acids and their related substances occur in the brain and have some physiological activity. These include taurine [107-35-7], serine, proline, pipecolic acid [535-75-1], N-acetyl-aspartic acid [997-55-7], α - and β -alanines, and L-cysteine sulfinic acid [2381-08-0]. For more details about neurotransmitter amino acids, see reference 112.

Modification of Amino Acid in Protein Molecules. Protein kinases, whose activities are regulated by secondary messengers, such as cyclic nucleotide and Ca^{2+} , modify physiologically important proteins by phosphorylating the hydroxy moiety of serine, threonine, and tyrosine in protein molecules. Consequently, various cellular functions, cell growth, and cell differentiation are seriously affected (113). Because the intracellular pool of secondary messengers is under the control of hormones, growth factors, and neurotransmitters, protein phosphorylation is also regulated by these signal compounds.

The participation of protein kinases in oncogenesis has been suggested (114). Thus some oncogenes (src, fps, yes, mos) are known to encode for protein kinases. Formation of some cross-links within molecules of proteins which are physiologically important and have a slow turnover rate (such as collagen) is believed to correlate seriously with aging of animal tissue. Nonenzymatic glycation of protein by the Maillard reaction possibly acts by such cross-link formation. L-Lysine and L-hydroxylysine moieties in a collagen molecule are often oxidized to their corresponding aldehydes by the action of lxyoxidase. Aldehydes react with the amino groups of L-lysine or L-hydroxylysine in the adjacent collagen molecules to form Schiff-base cross-links among the different collagen molecules. β -Aminopropionitrile [151-18-8] inhibits the oxidase reaction. Pyridinoline [63800-01-1] (9) and histidinoalanine [65428-77-5] (10) are also found as cross-linkers in collagen. The relationship between the aging of animal tissues and these cross-linking agents has been discussed (115).

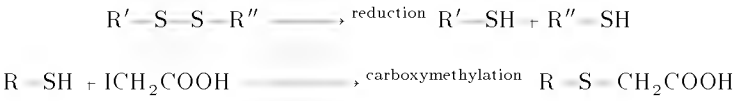


Analysis

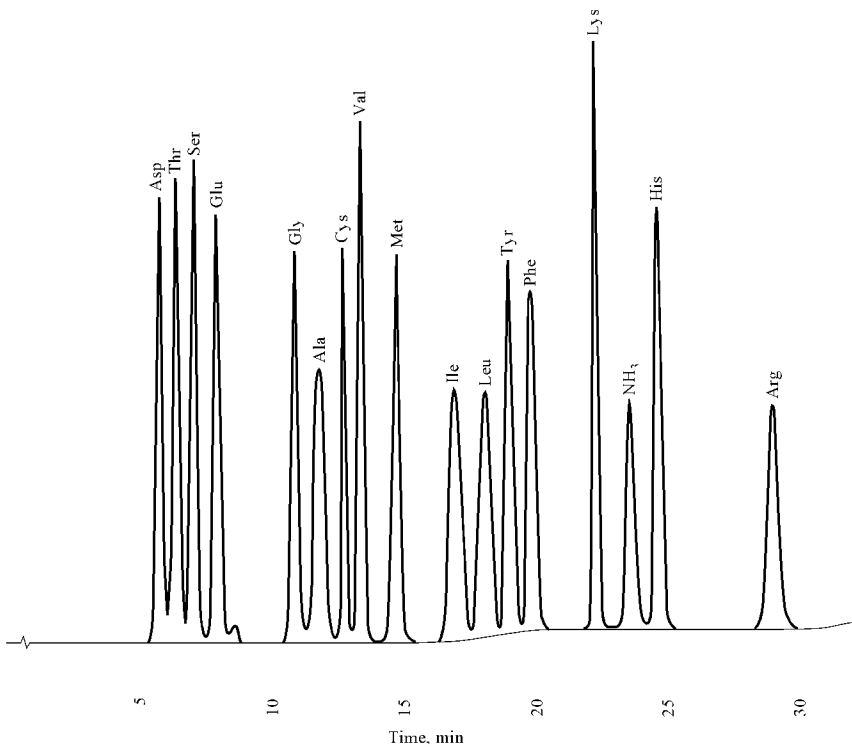
Methods have been developed for analysis or determination of free amino acids in blood, food, and feedstocks (116). In proteins, the first step is hydrolysis, then separation if necessary, and finally, analysis of the amino acid mixture.

Protein Hydrolysis. Acid hydrolysis of protein by 6 M HCl in a sealed tube is generally used (110°C, 24-h). During hydrolysis, slight decomposition takes place in serine (ca 10%) and threonine (ca 5%). Cystine and tryptophan in protein cannot be determined by this method because of complete decomposition.

For determination of tryptophan, 4 M methanesulfonic acid hydrolysis is employed (18). For cystine, the protein is reduced with 2-mercaptoethanol, the resultant cysteine residue is carboxymethylated with iodoacetic acid, and then the protein sample is hydrolyzed. Also, a one-pot method with mercaptoethanesulfonic acid has been developed for tryptophan and cystine (19).



The automated amino acid analyzer depends on ion-exchange chromatography (117) and is now a routine tool for the analysis of amino acid mixtures (118). This most advanced machine can detect as little as 10 pmol in ninhydrin reaction analysis. One-half to two hours are required for each analysis. An analysis chart is shown in Figure 2.



Name	RT	Height	Area	Ratio
Asp	5.81	32764	556900	1699.7
Thr	6.44	34036	592872	1741.8
Ser	7.10	35493	591477	1666.4
Glu	8.02	31380	568744	1812.4
Gly	10.92	28436	574689	2020.9
Ala	11.85	20527	529589	2579.9
Cys	12.81	28942	313874	1084.4
Val	13.45	38240	555963	1453.8
Met	14.77	28544	586978	2056.3
Ile	17.02	18485	538596	2913.6
Leu	18.17	17819	530384	2976.5
Tyr	19.08	27625	519627	1881.0
Phe	19.93	25061	538429	2148.4
Lys	22.33	44070	612254	1389.2
NH ₃	23.69	16393	376220	2295.0
His	24.73	31333	586159	1870.7
Arg	29.13	16421	484608	2951.1

Fig. 2. Amino acid analysis by automated ion-exchange chromatography. Standard column, 4.6 mm ID × 60 mm; Ninhydrin developer. Computer print out indicates retention time (RT), height and area of peaks, and the ratio of the height of an amino acid in the sample to the height of a standard amino acid. The number of ng in a 2 nmol sample of each amino acid is also tabulated (not shown here).

Individual analyses for each amino acid have also been established (119), in particular, Edelhoch spectrometric analysis for tryptophan (120) and Ellman colormetric analysis (121) for cysteine are often used.

Chromatographic Methods.

High Performance Liquid Chromatography (hplc). Hplc is currently the fastest growing analytical method and is now available in many laboratories. DL-Analysis by hplc has already been described and hplc methods have been reviewed (122).

Gas Chromatography (gc). A principal advantage of gas chromatography has been the facility with which it can be combined with mass spectrometry for amino acid identification and confirmation of purity. The gc-mass spectrometry combination offers the advantage of obtaining structural information rather than the identification by retention time in hplc.

Successful analysis of amino acids with gas chromatography is dependent on the synthesis of derivatives that are stable, yet volatile (123). The first step is esterification. A variety of alcohols have been used for esterification, including methanol, *n*-propanol, 2-propanol, *n*-butanol, and isobutyl alcohol, as well as some optically pure alcohols, eg, (+)butan-2-ol, (+)octan-2-ol. The next step is *N*-acylation by the addition of acetic anhydride, trifluoroacetic anhydride (TFAA), pentafluoropropionic anhydride (PFPA) or heptafluorobutyric anhydride (HFBA), along with an appropriate solvent. Alkylsilylation which has the advantage of being a fast, one-step derivatization for all groups commonly encountered (NH, OH, SH, COOH) is a useful tool for mass spectrometry. Trimethyl-silylation also is well-suited to chromatographic studies.

The synthesis and the quantitative gas chromatographic analysis of stable, yet volatile, *N*-trifluoroacetyl-*n*-butyl esters of amino acids has been established (124). An extensive review of subsequent advances in gas chromatographic instrumentation has been provided (125).

Thin-Layer Chromatography (tlc). Tlc (126) is used widely for qualitative analysis and micro-quantity separation of amino acid mixtures. The amino acids detected are developed by ninhydrin coloring, except for proline and hydroxyproline. Isatin has been recommended for specific coloring of proline (127).

Colorimetric and Fluorimetric Analysis. The functional groups of amino acids exhibit little absorption of uv light from 210 to 340 nm where uv absorption spectrometry is most conveniently conducted. Thus color or fluorescence formation reactions are employed for amino acid detection (128).

The most widely applied colorimetric assay for amino acids relies upon ninhydrin-mediated color formation (129). Fluorescamine [38183-12-9] and *o*-phthalaldehyde [643-79-8] are popular as fluorescence reagents. The latter reagent, in conjunction with 2-mercaptoethanol, is most often used in post-column detection of amino acids separated by conventional automated amino acid analysis. More recently, determination by capillary zone electrophoresis has been developed and it is possible to determine attomole quantities of amino acids (130).

Spectrometric Analysis. Remarkable developments in mass spectrometry (ms) and nuclear magnetic resonance methods (nmr), eg, secondary ion mass spectrometry (sims), plasma desorption (pd), thermospray (tsp), two or three dimensional nmr, high resolution nmr of solids, give useful structure analysis information (131). Because nmr analysis of ¹³C- or ¹⁵N-labeled amino acids enables determination of amino acids without isolation from organic samples, and without destroying the sample, amino acid metabolism can be dynamically analyzed (132). Protein metabolism and biosynthesis of many important metabolites have been studied by this method. Preparative methods for labeled compounds have been reviewed (133).

Enzymatic Determination and Microbial Assay. In these methods, only the desired amino acid is detected in spite of the presence of other amino acids. No expensive tools are needed for these determinations. The required nutrients for microorganisms and practical operations for the microbial assay of amino acids have been reviewed (134,135).

Manometric determination of L-lysine, L-arginine, L-leucine, L-ornithine, L-tyrosine, L-histidine, L-glutamic acid, and L-aspartic acid has been reviewed (136). This method depends on the measurement of the carbon dioxide released by the L-amino acid decarboxylase which is specific to each amino acid.

A kit for the enzymatic determination of L-glutamic acid has been commercialized. Hydrogen peroxide, which is formed through the L-glutamic acid oxidase reaction, is determined by coupling with the peroxidase reaction which forms a blue color complex in the presence of 4-aminoantipyrine [83-07-8] and *N*-hydroxysulfolpropylate. The oxidase reactions are applied to amino acid sensors, which have been commercialized recently for the determination of L-glutamic acid, L-lysine, or mixtures of L-amino acids. The amount of oxygen consumed by the reaction is electrically determined. It is possible to determine amino acids through the NAD-dependent dehydrogenase reaction which is specific to the corresponding amino acid (137). For the details of the enzymatic determination of amino acids, see reference 136.

Manufacture and Processing

Since the discovery of amino acids in animal and plant proteins in the nineteenth century, most amino acids have been produced by extraction from protein hydrolyzates. However, there are many problems in the efficient isolation of the desired amino acid in the pure form.

DL-Alanine is the first amino acid which was synthesized chemically (138). Glycine and DL-methionine have also been supplied by this method (20). However, amino acids formed by the chemical method are racemic, and it is necessary to resolve the mixture to get the L- or D-form amino acid which is usually demanded.

In the 1950s, a group of coryneform bacteria which accumulate a large amount of L-glutamic acid in the culture medium were isolated (21). The use of mutant derivatives of these bacteria offered a new fermentation process for the production of many other kinds of amino acids (22). The amino acids which are produced by this method are mostly of the L-form, and the desired amino acid is singly accumulated. Therefore, it is very easy to isolate it from the culture broth. Rapid development of fermentative production and enzymatic production have contributed to the lower costs of many protein amino acids and to their availability in many fields as economical raw materials.

Direct Fermentation Process. In this process, the microorganisms are cultured in the medium containing carbohydrates (eg, cane molasses, sucrose, glucose, starch hydrolyzate), acetic acid, alcohols (eg, ethanol, methanol) or hydrocarbons (eg, *n*-paraffin) as carbon sources, and nitrogen sources (eg, liquid ammonia, urea, ammonium salt), and minor nutrients [phosphate, sulfate, metal ions (K⁺, Mg²⁺, Fe²⁺, Ca²⁺ etc.), and if necessary, other growth factors (eg, vitamins, amino acids)]. The amino acid-producing microorganisms metabolize the carbon source and the nitrogen source via the pathways shown in Figure 3 to overproduce and accumulate amino acids in the culture medium. Figure 4 exemplifies the time course of L-glutamic acid production with *Corynebacterium glutamicum*. A flow sheet of fermentative production of amino acids is shown in Figure 5. The amount and the kinds of amino acids accumulated depend on the trait of microbial strains used and the culture conditions (such as medium composition, pH, temperature, aeration, agitation) (22). At present, cane molasses and starch hydrolyzate have been used as carbon sources in the manufacture of amino acids. As can be seen in Table 6 which lists, the amino acid production from carbohydrate, the microorganisms which produce amino acids in high amounts (enough to use for manufacture), are very few: (1) So called "glutamic acid bacteria" (141) (eg, *Corynebacterium glutamicum*, *Brevibacterium flavum*, *Brevibacterium lactofermentum*, (2) Enteric bacteria (eg, *Serratia marcescens*, *E. coli*); and (3) *Bacillus* sp. (eg, *Bacillus subtilis*). Among these, the glutamic acid bacteria can produce some amino acids from acetic acid and ethanol in high amount and these have been used widely as the carbon source (142). Ethanol alone has not been used. The bacteria which can assimilate hydrocarbons (C₁₁₋₁₄ kerosenes are favorable) have been isolated independently of the ones described above. As shown in Table 7, the mutant derivatives of *Arthrobacter*, *Corynebacterium*, *Brevibacterium*, and *Nocardia* species have been known to produce a large amount of many kinds of amino acids (157). However, these have not been used in actual production at present. The mutant derivatives of methanol assimilating bacteria belonging to *Pseudomonas*, *Arthrobacter*, *Methylobacter*, *Protaminobacter*, *Microcylus* (most of these are recently named *Methylobacillus glycogenes* (161)) have been isolated and their accumulation of L-glutamic acid (162), L-leucine, L-valine, L-isoleucine, and L-phenylalanine (161) have been reported. Recently, an L-lysine producing mutant of *Bacillus* sp., a thermophilic methylotroph, has been reported (163). However, the yield of the production is not high enough for manufacture at present.

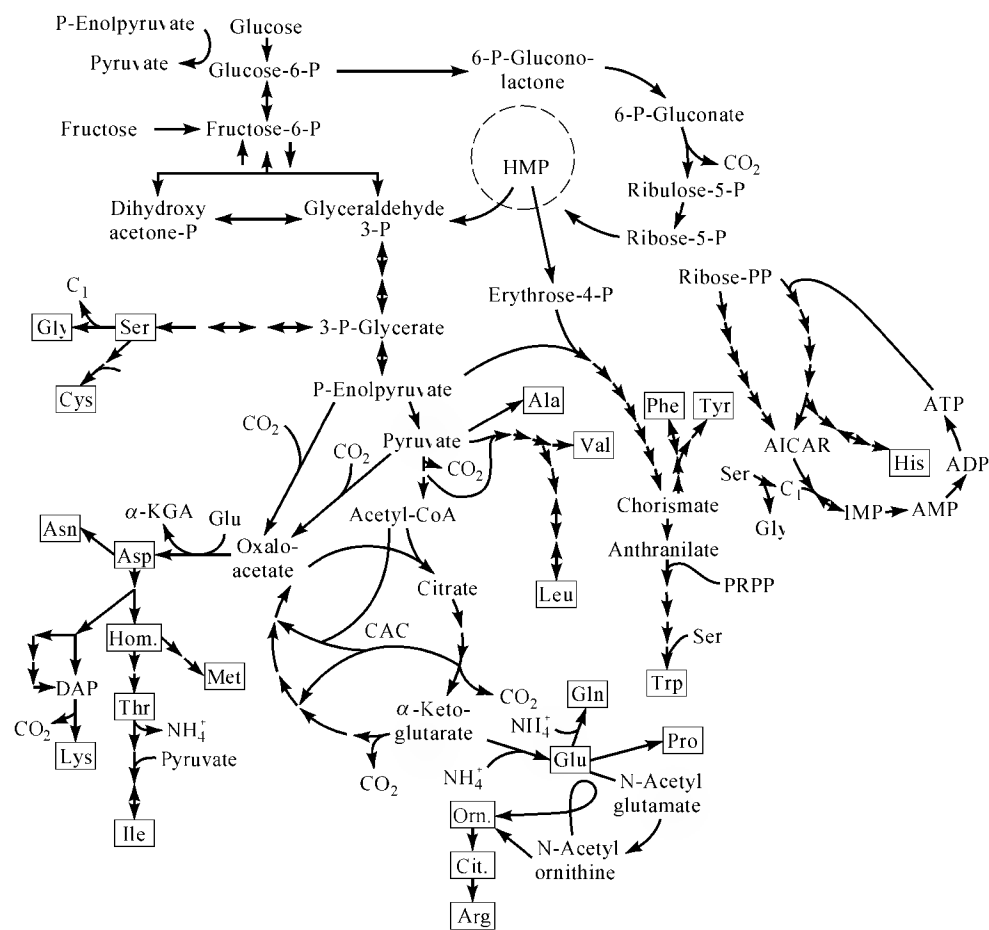


Fig. 3. Biosynthetic pathways for amino acids. HMP = hexose monophosphate pathway; CAC = citric acid cycle; P = phosphate; PP = pyrophosphate; AMP, ADP, and ATP = adenosine mono-, di-, and triphosphate; IMP = inosine 5'-monophosphate; AICAR = 5'-phosphoribosyl-5-amino-4-imidazolecarboxamide; DAP = diaminopimelic acid; PRPP = phosphoribosyl pyrophosphate; α - KGA = α-ketoglutaric acid; Orn = ornithine; Cit = citrulline; C₁ represents the one carbon unit lost to tetrahydrofolate as serine is converted to glycine.

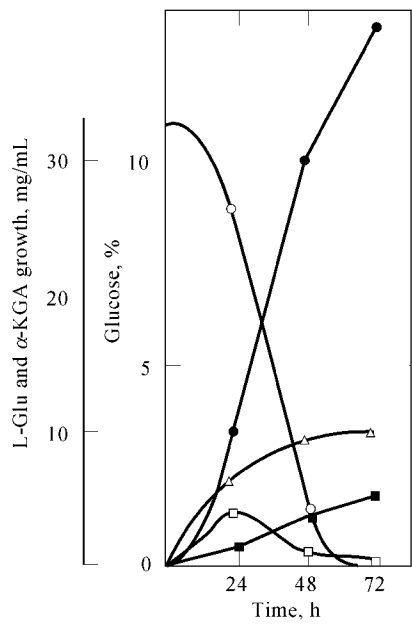


Fig. 4. L-Glutamic acid (and α-ketoglutaric acid, α-KGA) production by a wild type *Corynebacterium glutamicum* (139). The fermentation was carried out with a medium containing 10% glucose, 0.05% KH₂PO₄, 0.05% K₂HPO₄, 0.025% MgSO₄·7 H₂O, 0.001% FeSO₄·7 H₂O, 0.001% MnSO₄·4 H₂O, 0.5% urea, and 2.5 μg L biotin under aeration and agitation. The pH of the medium was controlled by adding urea during fermentation. ●, L-glutamic acid; ○, glucose; □, lactic acid; Δ, growth (dry cell weight); ■, α-ketoglutaric acid.

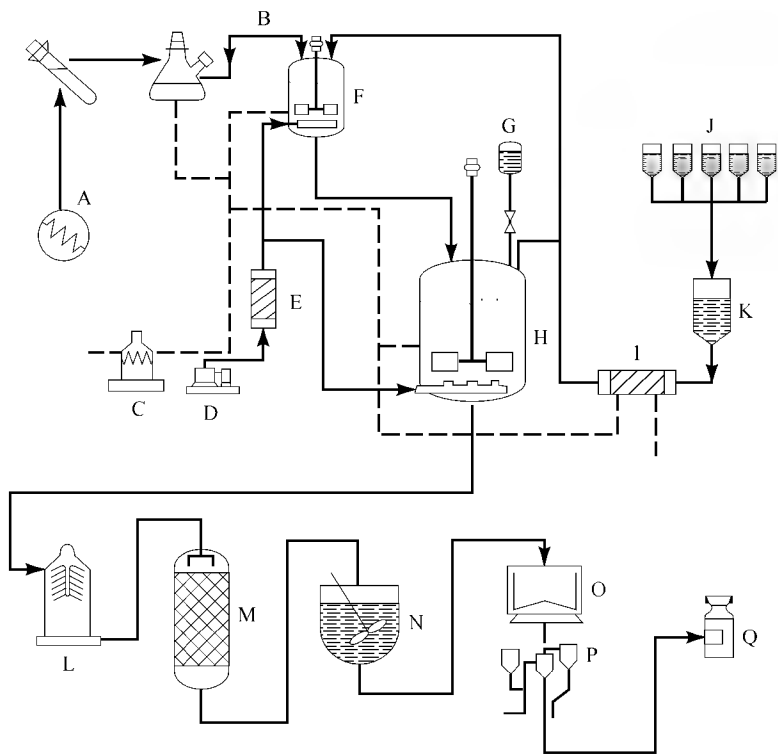


Fig. 5. Fermentative production of amino acids (140). A, pure culture; B, inoculation; C, boiler; D, air compressor; E, air filter; F, seed tank; G, ammonia water for pH control; H, fermenter; I, sterilizer; J, culture media; K, preparation tank; L, centrifugal separator; M, ion-exchange column; N, crystallizing tank; O, crystal separator; P, dryer; Q, amino acid production.

The pathway for amino acid biosynthesis is regulated at the key enzyme mainly by two regulation mechanisms—feedback inhibition (inhibition of enzyme activity usually by the end product of the pathway) and repression (repression of enzyme formation usually by the end product) (164). These prevent the overproduction of amino acids in the wild-type microbial cells. Amino acid production is attained by selecting favorable culture conditions, and or changing the bacterial trait through mutational or other genetic treatment to overcome the feedback regulations and induce the overproduction and excretion of amino acids outside the cells (22). Production of L-glutamic acid (158), L-glutamine (165), and L-proline (166) by wild-type glutamic acid bacteria are typical examples of the effect of controlling the culture condition. The limited addition of biotin [58-85-5], a growth factor, or the addition of penicillin (or other β -lactam antibiotics) to the culture induce the accumulation of a large amount (80 mg mL or more) of L-glutamic acid in the culture medium. Other strains of glutamic acid bacteria accumulate L-proline or L-glutamine when NaCl is added to the medium in a high concentration (eg, 6%).

Table 6. Fermentative Production of Amino Acids and Their Related Substances from Carbohydrates^a

Microorganisms	Primary mutation ^b	Genetic markers ^b or culture conditions which enhance productivity	Yield, mg mL (and or %)	References
<i>L-Glutamic acid</i>				
"glutamic acid bacteria" such as <i>Coryneb. glutamicum</i> , <i>Brevib. flavum</i> , <i>Brevib. lactofermentum</i> , <i>Microb. ammoniaphilum</i>	wild	penicillin is added, or biotin is limited	>100, 50%	21
<i>Brevib. thiogenitalis</i>	oleic acid	production from acetic acid and Cu ²⁺ is effective	66, 50%	
<i>Coryneb. alkanolyticum</i>	glycerol		40%	
<i>B. lactofermentum</i>	temperature ^s		50%	
<i>C. glutamicum</i>	lysozyme ^s			143
<i>B. flavum</i>	vitamin P ^t			
(N-acetyl-L-glutamic acid) <i>C. glutamicum</i>	arg		7.5	
(N-acetylglutamic- γ -semialdehyde) <i>C. glutamicum</i>	arg		2.7	
(L-glutamic- γ -semialdehyde) <i>B. flavum</i>	pro	sulfite is effective	13.2	144
<i>L-Glutamine</i>				
"glutamic acid bacteria"	wild	high concentration of NaCl is effective	>44	
<i>Flavobacterium rigens</i>	ser	ammonium fumarate is added	25	
<i>B. flavum</i>	sulfaguanidine ^t		40	
(N-acetyl-L-glutamine) "glutamic acid bacteria"	wild		20%	
<i>L-Proline</i>				
<i>B. flavum</i>	ile ; 3,4-dehydro-Pro ^t			
<i>Brevibacterium</i> sp.	his		25.5	
<i>C. glutamicum</i>	wild	high concentration of NH ₄ Cl is effective	40	
<i>Kurthia cateniforma</i>	ser	Asp is added	30	
<i>Serratia marcescens</i>	3,4-dehydro-Pro ^t	prodegradation , thiazoline-4-carboxylate ^t , azetidine-2-carboxylate ^t (transduction)	75	145
<i>Coryneb. melassecola</i>	tyr , phe			
<i>L-Arginine</i>				
<i>B. flavum</i>	2-thiazole-3-Ala ^t	Guanine	35	
<i>C. glutamicum</i>	D-Ser ^s	D-Arg ^t , Arg-hydroxamate ^t , 2-thiazole-3-Ala ^t ; continous culture is effective	60	146
<i>B. subtilis</i>	Arg-hydroxamate ^t	6-azauracil ^t	28	

<i>S. marcescens</i>	Arg-degradation , argR , argA	succinate nonassimilating, 6-azauracil [†] (transduction)	100	
<i>L-Citrulline</i>				
<i>C. glutamicum</i> , <i>B. flavum</i>	arg		16	
<i>B. subtilis</i>	arg	Arg-analogue [†] , 6-azauracil [†]	26	
<i>L-Ornithine</i>				
<i>C. glutamicum</i> , <i>B. flavum</i> , <i>B. subtilis</i> (<i>N</i> ⁶ ;-acetyl-L-ornithine)	arg		36 ⁰ o	
<i>Paracolobactrum coliforme</i>	arg , uracil			
<i>B. subtilis</i>	Arghydroxamate [†]			
<i>Streptomyces virginiae</i> (<i>N</i> ^α ;-acetyl-L-ornithine)	lys		11	
<i>C. glutamicum</i>	arg		1.2	
<i>L-Lysine</i>				
<i>C. glutamicum</i>	hom (Thr , Met)	leu , AEC [†] , pyrimidine-analogue [†] , Asp-analogue [†] ; contenious culture is effective	100	147
<i>B. flavum</i>	hom (Thr , Met)	AEC [†] , 2-fluorophyruvic acid [‡] , pyruvate kinase [±]	40 ⁰ o	148
<i>B. lactofermentum</i>	AEC [†]	leu , ala , 2-fluoropyruvic acid [‡]	50, 30 ⁰ o	
<i>B. lactofermentum</i>	AHV [†]		16 ⁰ o	
<i>S. marcescens</i>	Lys decarboxylase , hydroxy-Lys [†] , Lys · hydroxamate [†]		6.5	
<i>Candida pelliculosa</i> (<i>N</i> ^ε ;-acetyl-L-lysine)	AEC [†]		3.2	
<i>C. hydrocarboclastus</i> (ε-Polylysine)	AEC [†]	phe ⁺	23	
<i>Streptomyces albus</i> , <i>S. noursei</i>	wild	AEC [†] , hom (Met , Thr); addition of Lys is effective	20.3	149
α-εDiaminopimelic acid (DAP)				
<i>E. coli</i> , <i>C. glutamicum</i> , <i>B. subtilis</i> , <i>Brevib. ammoniagenes</i> (N-succinyl-DAP)	lys		25	
<i>A. aerogenes</i> , <i>S. marcescens</i>	DAP		20	
<i>L-Homoserine</i>				
<i>C. glutamicum</i> , <i>E. coli</i> , <i>B. flavum</i> (O-acetyl-L-homoserine)	thr		15	
<i>Bacillus</i> sp.	met		1	
<i>L-Threonine</i>				
<i>E. coli</i>	met , DAP	ile , AHV [†] , Thr-degradation , rifampicin [†] , Lys [†] , Met [†] , Asp [†]	76	150
<i>E. coli</i>	AHV [†]	hom , ile , met	55	
<i>B. lactofermentum</i>	AHV [†]	AEC [†] , S-methyl-Cyshydroxamate [†] , ile , leu	25	
<i>C. glutamicum</i>	AHV [†]	met	14	
<i>S. marcescens</i>	AHV [†]	Thr-degradation , ile , AEC [†] (transduction)	40	
<i>Providencia rettgerii</i>	ile , AHV [†]	ethionine [†] , Asphydroxamate [†] , leu ,	82	151
<i>B. flavum</i>	AHV [†]	Thr-degradation , Thia-Ile [†]	16.7	
<i>Proteus rettgerii</i>	ile , AHV [†]	dihydropicolinate synthase	13	
<i>Candida guilliermondii</i>	ile , met , trp		4	
<i>L-Methionine</i>				
<i>C. glutamicum</i>	thr , ethionine [†]		2	
<i>L-Aspartic acid</i>				
<i>B. flavum</i>	diaminopurine [†]		10	
<i>B. flavum</i>	glu [±]			
<i>D-L-Alanine</i>				
<i>C. gelatinosum</i> , <i>B. pentosaminoacidicum</i> , <i>Fusarium moniliforme</i> etc	wild		40	
<i>M. ammoniaphilum</i> (<i>L-Alanine</i>)	Arghydroxamate	addition of lactic acid is effective	60	
<i>Pseudomonas</i> sp.	wild			
<i>C. glutamicum</i> (<i>D-Alanine</i>)	Ala racemase			
<i>Coryneb. fasciens</i>	wild			
<i>B. lactofermentum</i>	D-cyclo-Ser [†]	addition of D-L-Ala is effective	48	152
<i>L-Isoleucine</i>				
<i>S. marcescens</i>	Ilehydroxamate [†]	α-aminobutyric acid [†] , lys C [†] , thr A	25	
<i>B. flavum</i>	AHV [†]	O-methyl-Thr [†] , ethionine [†]	34	
<i>C. glutamicum</i>	Thia-Ile [†]	AHV [†] , Aza-Leu [†] , α-aminobutyric acid [†]	10	
<i>L-Leucine</i>				
<i>S. marcescens</i>	α-aminobutyric acid [†]	ile	15	
<i>B. lactofermentum</i>	2-thiazole-3-Ala [†]	met , ile	30	
<i>C. glutamicum</i>	AEC [†]		20	
<i>L-Valine</i>				
<i>P. coliforme</i> , <i>E. coli</i> , <i>A. aerogenes</i> , <i>B. ammoniagenes</i>	wild		7–12, 23 ⁰ o	
<i>C. glutamicum</i>	ile , leu		30	
<i>S. marcescens</i>	α-aminobutyric acid		8	
<i>B. lactofermentum</i>	2-thiazole-3-Ala [†]		31	
<i>C. glutamicum</i>	AEC [†]		20	

<i>L-Tryptophan</i>				
<i>B. flavum</i>	5-fluoro-Trp ⁱ	<i>m</i> -fluoro-Phe ^s , phe ⁻ , tyr ⁻ , Aza-Ser ⁱ	10	153
<i>C. glutamicum</i>	phe ⁻ , tyr ⁻ , 5-methyl-Trp ⁱ	Trphydroxamate ⁱ , 4-methyl-Trp ⁱ , ppc ⁻ ; gene technology is effective	45	
<i>B. subtilis</i>	5-fluoro-Trp ⁱ	indolemycin ⁱ , Aza-Ser ⁱ , 6-diazo-5-oxonordeucine ⁱ	21.5	
<i>E. coli</i>	5-fluoro-Trp ⁱ	gene technology is effective; addition of detergent is effective	40	154
<i>L-Tyrosine</i>				
<i>C. glutamicum</i>	phe	3-amino-Tyr ⁱ , <i>p</i> -amino-Phe ⁱ , <i>p</i> -fluoro-Phe ⁱ , Tyrhydroxamate ⁱ	17.6	
<i>B. flavum</i>	phe	<i>m</i> -fluoro-Phe ⁱ		
<i>L-Phenylalanine</i>				
<i>B. lactofermentum</i>	tyr	<i>p</i> -fluoro-Phe ⁱ , 5-methyl-Trp ⁱ , decoinine ⁱ	25	
<i>C. glutamicum</i>	tyr	<i>p</i> -fluoro-Phe ⁱ	9.5	
<i>L-Serine</i>				
<i>C. glycinophilum</i>	sulfaguanidine ⁱ		4.5	
<i>L-Histidine</i>				
<i>C. glutamicum</i>	2-thiazole-3-Ala ⁱ ; triazole-Ala ⁱ ; 2-fluoro-His ⁱ	purine and pyrimidine analogues ⁱ	15	
<i>B. flavum</i>	2-thiazole-3-Ala ⁱ	sulfa drugs ⁱ , AEC ⁱ	10	
<i>S. marcescens</i>	2-methyl-His ⁱ , Triazole-Ala ⁱ	His degradation (transduction)	23	
<i>B. subtilis</i>	5-fluoro-Trp ⁱ , tri-his	dimethyltriazaindolidine ⁱ , 2-thiazole-3-Ala ⁱ	13.6	
<i>Streptomyces coelicolor</i> (L-Histidinol)			3.5	
<i>B. flavum</i>	his		8	
<i>C. glutamicum</i>	his		10	

^a Refs. 21, 22, 155.

^b Abbreviations: AHV, α -amino- β -hydroxyvaleric acid; Hom, L-homoserine; AEC, (*S*-(2-aminoethyl)-L-cysteine; ppc, phosphoenolpyruvate carboxylase; the strain improvement largely depends on the transduction technology; ^s, sensitive; ⁱ, resistant; ⁻, auxotroph or deficient; [±], leaky auxotroph; ⁺, prototrophic revertant.

Table 7. Amino Acid Production from Hydrocarbons^a

Amino acid produced	Microorganisms	Characteristics ^b of amino acid producers	Amount of accumulation, mg mL
L-glutamic acid ^c	<i>Arthrobacter paraffineus</i> , <i>Coryneb. hydrocarboclastus</i> , <i>Coryneb. alkanolyticum</i> etc	wild	84
L-ornithine	<i>C. hydrocarboclastus</i> , <i>A. paraffineus</i>	glycerol	
L-citrulline	<i>Corynebacterium</i> sp.	arg cit	9
L-lysine (N-acetyl-L-lysine) ^d	<i>Brevibacterium ketoglutamicum</i> , <i>Nocardia</i> sp.	arg	8
	<i>C. hydrocarboclastus</i>	hom	75
diaminopimelic acid	<i>A. paraffineus</i>	AEC ⁱ , his	41
L-serine	<i>A. paraffineus</i>	lys	10
L-threonine	<i>A. paraffineus</i>	ile	3
L-homoserine	<i>Corynebacterium</i> sp.	ile	27
DL-alanine	<i>C. hydrocarboclastus</i>	thr	12
L-valine	<i>A. paraffineus</i>	wild	4
L-isoleucine	<i>Microbacterium paraffinolyticum</i>	ile	5
L-tyrosine ^e	<i>A. paraffineus</i>	val , leu	1.6
L-phenylalanine ^e	<i>A. paraffineus</i>	phe	18
		tyr	15

^a Ref. 23, 157.

^b Abbreviations: Hom, homoserine; AEC, *S*-(2-aminoethyl)-L-cysteine; ⁱ, resistant; ⁻, auxotroph.

^c Ref. 158.

^d Ref. 159.

^e Ref. 160.

Many kinds of amino acids (eg, L-lysine, L-ornithine, L-phenylalanine, L-threonine, L-tyrosine, L-valine) are accumulated by auxotrophic mutant strains (which are altered to require some growth factors such as vitamins and amino acids) (Table 6, Primary mutation) (22). In these mutants, the formation of regulatory effector(s) on the amino acid biosynthesis is genetically blocked and the concentration of the effector(s) is kept low enough to release the regulation and induce the overproduction of the corresponding amino acid and its accumulation outside the cells (22).

The amino acids (eg, L-arginine, L-histidine) that are synthesized by a straight line biosynthetic pathway are overproduced by the regulatory mutants in which the feedback regulations are genetically released. These mutants are easily selected among the mutants that are resistant to the growth inhibition of the amino acid analogue (whose chemical structure closely resembles the amino acid and falsely regulates the amino acid biosynthesis) (22). Many other amino acids (eg, L-isoleucine, L-leucine, L-lysine, L-proline, L-threonine, L-tryptophan, L-valine) are also overproduced by the analogue resistant mutants as well as the auxotrophic mutants (22).

Amino acid producing strains do not always produce amino acids efficiently enough to be useful for manufacture. Mutant strains are usually improved by combined additions of various genetic markers including other kinds of auxotrophy, analogue resistance, etc (Table 6). These mutations, which increase the amino acid productivity, not only include those which cause deregulation of biosynthesis, but also mutations which make the metabolic flow more efficient to produce the desired amino acid (22,148). The mutations which cause elimination of degradation enzymes and a permeability barrier for the amino acid are, if these are serious, important to improve the amino acid producers. L-Glutamic acid, L-glutamine, L-proline, L-arginine, L-ornithine, L-lysine, L-isoleucine, L-threonine, L-leucine, L-valine, L-tyrosine, L-phenylalanine, L-tryptophan, and L-histidine have been manufactured by fermentation processes.

Advanced biotechnologies such as cell fusion and gene technology are powerful tools offering improvements (167,168). By cell fusion technology, L-lysine and L-isoleucine production of glutamic acid bacteria has been improved (169). The transduction method is very useful for strain breeding because it is very easy to introduce excellent genetic markers to the amino acid producers (170). The L-histidine, L-arginine, L-threonine, L-proline, and L-isoleucine producers of *Serratia marcescens* have been skillfully improved by this method using phage PS 20. The bred strains have been used in the manufacture of those amino acids.

Since 1982, the gene multiplication method with plasmid vectors has been applied to the breeding of amino acid producers. To the plasmid vector which can multiply in the amino acid producers, the DNA fragment carrying the genetic information of the other strains of the same or other microorganisms is joined enzymatically, and the resultant recombinant DNA is transferred to the amino acid producers to introduce the new markers due to the donor microorganisms (167,168,171). As exemplified in Table 8, great advances have been made in *C. glutamicum*, *B. lactofermentum*, *S. marcescens*, *B. subtilis*, and *E. coli*.

Table 8. Breeding of Amino Acid Producers by Gene Technology^a

Amino acid produced	Microorganisms	Gene donor	Cloned gene ^b or enzyme	Yield mg m L	Reference
L-alanine	<i>E. coli</i>	<i>B. stearothermophilus</i>	Ala dehydrogenase		
D-alanine	<i>E. coli</i>	<i>Ochrobactrum anthropi</i>	D-aminopeptidase	200	174
L-aspartic acid	<i>E. coli</i>	<i>E. coli</i>	Asp A	^c	175
L-arginine	<i>S. marcescens</i>	<i>S. marcescens</i>	Asp A		
	<i>C. glutamicum</i>	<i>E. coli</i>	Arg E, C, B, H		
	<i>E. coli</i>	<i>E. coli</i>	Arg A		
L-glutamic acid	<i>C. melassecola</i>	<i>C. melassecola</i>	Glu A, citrate dehydrogenase, ppc, aconitate dehydratase		
L-histidine	<i>C. glutamicum</i>	<i>C. glutamicum</i>	Glu A	15	
	<i>C. glutamicum</i>	<i>C. glutamicum</i>	His G, D, C, B		
	<i>B. subtilis</i>	<i>B. subtilis</i>	His D	8.8	
	<i>S. marcescens</i>	<i>S. marcescens</i>	His G, D, B	43	
L-isoleucine	<i>C. glutamicum</i>	<i>C. glutamicum</i>	Hom dehydrogenase	11	
	<i>S. marcescens</i>	<i>S. marcescens</i>	ilv A		
	<i>B. flavum</i>	<i>E. coli</i>	ilv A	21	
L-lysine	<i>C. glutamicum</i>	<i>B. lactofermentum</i>	ilvB		
	<i>E. coli</i>	<i>B. lactofermentum</i>	lys A, asd-1		
	<i>E. coli</i>	<i>Achromob. obae</i>	α-Amino-ε-caprolactum racemase		
	<i>B. subtilis</i>	<i>B. subtilis</i>	Lys A		
	<i>C. glutamicum</i>	<i>C. glutamicum</i>	Lys A, dap A,B,D,Y		
	<i>B. flavum</i>	<i>B. flavum</i>	ppc		
	<i>C. glutamicum</i>	<i>E. coli</i>	Asp A		
	<i>C. glutamicum</i>	<i>C. glutamicum</i>	aro F, chorismate mutase, PRDH	28	
	<i>C. glutamicum</i>	<i>E. coli</i>	aro G, Phe A		
L-phenylalanine	<i>B. lactofermentum</i>	<i>B. lactofermentum</i>	aro F, E, L, PRDH	21	
	<i>E. coli</i>	<i>E. coli</i>	aro F, Phe A	28.5	
	<i>E. coli</i>	<i>E. coli</i>	transaminase		
	<i>E. coli</i>	<i>C. freuindii</i>	transaminase		
	<i>E. coli</i>	<i>Paracoccus denitrificans</i>	transaminase		
	<i>E. coli</i>	<i>B. stearothermophilus</i> , <i>Sporosarcina ureae</i> , <i>B. sphaeroides</i>	Phe dehydrogenase		
	<i>E. coli</i>	<i>Rhodotorula rubra</i>	Phe ammonialyase		176
	<i>S. marcescens</i>	<i>S. marcescens</i>	Pro A, B	75	145
	<i>E. coli</i>	<i>E. coli</i>	Gly A		
	<i>E. coli</i>	<i>E. coli</i>	Ser A, B, C	1.2	
L-threonine	<i>C. glutamicum</i>	<i>C. glutamicum</i>	Gly A		177
	<i>E. coli</i>	<i>E. coli</i>	Thr A, B, C	55	178
	<i>C. glutamicum</i>	<i>E. coli</i>	asp kinase, hom dehydrogenase, hom kinase, Thr C	21	
L-tryptophan	<i>C. glutamicum</i>	<i>C. glutamicum</i>	hom dehydrogenase, hom kinase, Thr C	51	179
	<i>B. lactofermentum</i>	<i>B. lactofermentum</i>	ppc, hom dehydrogenase, hom kinase	33	180
	<i>B. flavum</i>	<i>E. coli</i>	Thr B, C	27	
	<i>S. marcescens</i>	<i>E. coli</i>	ppc	60	
	<i>B. subtilis</i>	<i>B. subtilis</i>	Trp B, C, F		
	<i>E. coli</i>	<i>E. coli</i>	Trp A, B, E, Ser B		
	<i>E. coli</i>	<i>E. coli</i>	Trp A, E, R, tna A	40	154
	<i>B. lactofermentum</i>	<i>B. lactofermentum</i>	ant-PR transferase, aro B, L, E; Trp	7.5	181
	<i>C. glutamicum</i>	<i>C. glutamicum</i>	A, B, C, D, E, G		
L-tyrosine			Trp E, aro F, chorismate mutase, PRDH	45	153
	<i>E. coli</i>	<i>Enterob. aerogenes</i>	Tna A		
	<i>E. coli</i>	<i>Alcalig. faecalis</i>	Tna A		
	<i>C. glutamicum</i>	<i>E. coli</i>	Aro F	9	
	<i>B. lactofermentum</i>	<i>B. lactofermentum</i>	Aro A		

^a Ref. 167, 168, 172.

^b Gene symbols are according to those of *E. coli*. (173). Abbreviations: Hom, Homoserine; Ant, Anthranilic acid; PR, Phosphoribosyl; ppc, Phosphoenolpyruvate carboxylase; PRDH, prephenate dehydrogenase.

^c 80-fold activity.

Semifermentation Process. In this process, the metabolic intermediate in the amino acid biosynthesis or the precursor thereof is added to the medium, which contains carbon and nitrogen sources, and other nutrients required for growth and production, and the metabolite is converted to the

Amino acid produced		Substrate	Enzyme	Enzyme source	Reference
			<i>L-Form amino acids</i>		
L-amino acids	DL-acetyl amino acids		L-aminoacylase	<i>Asp. oryzae</i>	25
	DL-amino acid carbamates			<i>Pseud. fluorescens</i>	191
L-alanine	L-aspartic acid		Aspartic-β-decarboxylase	<i>Pseud. dactynbæ</i> etc ^b	192
L-aspartic acid	pyruvic acid + NH ₄ ⁺ + NADH		Ala dehydrogenase		
	fumaric acid + NH ₄ ⁺		aspartase	<i>E. coli</i> ^b	
L-citrulline	L-arginine		Arg deiminase		
L-cysteine (derivatives)	β-chloro-DL-alanine + Na ₂ S (thiols)		Cys desulphydrase	<i>Enterobactor cloacae</i>	193
	L-serine(derivatives) + H ₂ S		Trp synthase	<i>E. coli</i> ^b	
L-cysteine	DL-2-aminothiazoline-4-carboxylic acid		hydrolase + racemase	<i>Pseud. thiazolinophilum</i> ^b	
	L-acetylserine + H ₂ S		acetylserine sulphydrylase		
L-cystathionine (derivatives)	L-homoserine + L-cysteine (derivatives)		cystathionine-γ-synthase	<i>Streptomyces phaeochromogenes</i>	
			cystathionine-α-lyase	<i>Ervi carotovora</i>	133
L-homoserine (derivatives)	L-homoserine + thiol(s)		L-methionine-γ-lyase	<i>Clostridium, Pseudomonas</i>	133
L-leucine	α-ketoisocaproic acid + NH ₄ ⁺ + NADH		Leu dehydrogenase	<i>Bacillus sphaericus</i> ^b	194,195
	DL-leucine amide			<i>Coryneb. metharica</i>	
	α-aminoisocapronitril			<i>Nocardia</i> sp.	196
L-3-methylvaline	3,3-dimethyl-2-oxobutyric acid + Asp		transaminase		197
				<i>Cryptococcus leurentii</i>	
L-lysine	DL-α-aminocaprolactum		hydrolase + Racemase	<i>Achromobactor obae</i> ^b	
	α,ε-diaminopimelic acid		DAP decarboxylase		
L-methionine	DL-methionine + Asp		D-amino acid oxidase + transaminase	<i>Trigonopsis variabilis</i>	
	α-keto-γ-methylthiobutyric acid + NH ₄ ⁺ + formic acid		Phe dehydrogenase + formate dehydrogenase	<i>Sporosarcina ureae</i>	195
L-ethionine	L-methionine + Na ₂ S		methioninase		
L-phenylalanine	<i>trans</i> -cinnamic acid + NH ₄ ⁺		Phe ammonialyase	<i>Rhodotolura glutinis, Endomyces linderi</i> etc. ^b	198
	phenylpyruvic acid + Asp (or NH ₄ -fumarate)		transaminase	<i>Citrobactor freuindii, E. coli</i> ^b	
	phenylpyruvic acid + NH ₄ ⁺ + formic acid		Phe dehydrogenase + formate dehydrogenase	<i>Brevibacterium</i> sp., <i>Rodccus</i> sp., <i>Sporosarcina ureae</i>	195,199
	DL-phenylalanine amide			<i>Coryneb. metharica</i>	
	DL-phenyllactic acid + NH ₄ ⁺		D- and L-hydroxyisocaproate dehydrogenase + Phe dehydrogenase dehydrogenase	<i>Lactobacillus casei</i>	
	DL-5-phenylhydantoin		hydantoinase + hydrolase	<i>Flavob. sp.</i>	
L-2-amino-4-phenylbutyric acid	acetoamidocinnamic acid		acylase + Phe dehydrogenase	<i>Brevib. sp.</i>	
	2-keto-4-phenylbutyric acid (KPBA) + Asp		transaminase		
	KPBA + formic acid + NH ₄ ⁺		Phe dehydrogenase + formate dehydrogenase		
L-α-methylphenylalanine	DL-α-methylphenylalanine amide			<i>Micobacterium</i> sp.	200
fluoro-L-phenylalanine	fluorophenylpyruvic acid + Asp		transaminase etc		
	fluoro- <i>trans</i> -cinnamic acid		Phe ammonialyase		
L-serine	glycine + formaldehyde		serine hydroxymethyltransferase ^b	<i>E. coli</i>	201
	DL-2-oxo-oxazolidine-4-carboxylic acid		hydrolase + racemase	<i>Pseud. testeroni</i>	
	D-glyceric acid + NH ₄ ⁺		glycerate dehydrogenase + Ala dehydrogenase		202
selenium amino acids	amino acid(s) + selenol(s)		methionine-γ-lyase		
L-tryptophan	indole + pyruvic acid + NH ₄ ⁺		tryptophanase	<i>Proteus rettgerii</i>	
	indole + DL-serine		tryptophanase + Ser racemase	<i>E. coli</i> <i>Pseud. putida</i> ^b	203
	indole + L-serine		Trp synthase	<i>E. coli</i>	
	DL-5-indorylmethylhydantoin		hydantoinase + hydrolase	<i>Flavobacterium</i> sp. ^b	204
	indole-3-pyruvic acid + NH ₄ ⁺ + NADH		Phe dehydrogenase		195
5-hydroxy-L-tryptophan	5-hydroxyindole + pyruvic acid + NH ₄ ⁺		tryptophanase		
fluoro-L-tryptophan	fluoroindole + pyruvic acid + NH ₄ ⁺		tryptophanase		
L-tyrosine	phenol + pyruvic acid + NH ₄ ⁺		β-tyrosinase	<i>Erwinia herbicola</i> ^b	
3,4-dihydroxy-L-phenylalanine	cathecol + pyruvic acid + NH ₄ ⁺		β-tyrosinase		
L-valine	α-ketoisovaleric acid + NH ₄ ⁺ formic acid		Phe dehydrogenase + formate dehydrogenase		195
			<i>D-Form amino acids</i> ^c		
D-amino acids	DL-acylamino acids		D-aminoacylase		206
D-alanine	DL-alanine hydantoin		D-hydantoinase + D-N-carbamylamino acid amidohydrolas	<i>Arth. crystallopoietes</i>	
	DL-alanine amide			<i>Arthrobactor</i> sp.	
D-alanine (peptides)	DL-alanine (peptide) amide(s)		D-amino acid aminopeptidase	<i>Ochrobactrum anthropi</i> , <i>Rhodococcus erythropolis</i> ^b	174
D-aspartic acid	DL-aspartic acid		asp-β-decarboxylase		
D-cysteine (derivatives)	3-chloro-DL-alanine + NaHS		3-chloro-D-Ala dehydrochlorinase or	<i>Pseudomonas putida</i> <i>E. coli</i> etc	

	(derivatives)	D-cysteine desulphydrase		
D-glutamic acid	L-glutamic acid	Glu decarboxylase + Glu racemase	<i>Lactobac. brevis</i>	207
D-methionine	DL-acetylmethionine	D-aminoacylase	<i>Alkaligenes denitrificans</i>	208
		+ acylamino acid racemase racemase	<i>Streptomyces sp.</i>	
D-phenylalanine	DL-phenylalanine amide	amidase	<i>Ochrobactrum anthropi,</i> <i>Rhodococcus erythropolis</i>	
D-phenylglycine	DL-phenylglycine amide	amidase		
N-carbamyl-D-phenylglycine	DL-5-phenylglycine hydantoin	hydantoinase	<i>Pseud. putida</i>	
N-carbamyl-D- <i>p</i> -hydroxyphenylglycine	DL- <i>p</i> -hydroxyphenylglycine hydantoin	hydantoinase	<i>Pseud. putida</i> ^b	
<i>p</i> -hydroxy-D-phenylglycine	<i>p</i> -hydroxy-DL-phenylglycine hydantoin	hydantoinase	<i>Pseud. putida</i>	209
N-carbamyl-D-valine	DL-valine hydantoin	hydantoinase		

^a Refs. 23, 24.
^b Chemical reactions are shown in Figure 6.
^c Refs. 24, 133, 205.

Table 11. Production^a and Price of Amino Acids

Amino acid	Method ^b	Production, t yr		Price ^c , \$ kg
		Japan	World	
DL-alanine	C	1,500		6–7
L-alanine	Enz	150		12–29
L-arginine	Ext, F	700	1,000	44–51
L-aspartic acid	Enz	2,000	4,000	10–12
L-asparagine	Ext	30		
L-citrulline	Enz	50		
L-cysteine and cystine	Ext, Enz	300	1,000	59–88
glycine	C	3,500	6,000	7–13
L-glutamic acid	F	80,000	340,000	3
L-glutamine	F	850		44–52
L-histidine	F	250		110–147
L-isoleucine	F	200		294–331
L-leucine	Ext, F	200		74–147
L-lysine	F	30,000	70,000	5–6
DL-methionine	C	30,000	250,000	5–6
L-methionine	Enz	150		74–88
L-ornithine	F	70		74–147
L-phenylalanine	C, F, Enz	1,500	3,000	59–88
L-proline	F	150		147–294
L-serine	F, Enz	60		74–132
DL-serine	C			
L-threonine	C, F	200		125–147
L-tryptophan	C, F, Enz	250		74–147
L-tyrosine	Ext, F	60		74–110
L-valine	C, F	200		110–147

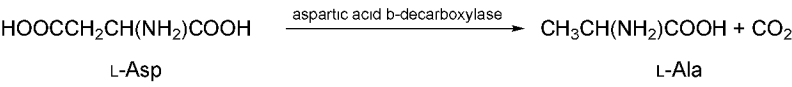
^a Ref. 218.
^b C, chemical synthesis; Enz, enzymatic synthesis; Ext, extraction; F, fermentation.
^c Ref. 219.

Uses

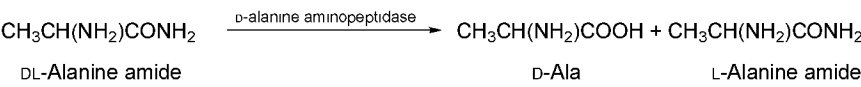
Amino acids are used in feeds (214), food (214), parenteral and enteral nutrition (93), medicine (215), cosmetics (216), and raw materials for the chemical industry (217).

In Feeds. The agricultural products which are used as feedstuff for domestic animals are different, as shown in Figure 7, depending on the areas where they are used. These feedstuffs do not always meet the essential amino acid requirements for the economical growth of the animals and usually require DL-methionine and L-lysine supplements as the first and or second limiting amino acid as shown in Table 12. The world consumption of DL-methionine and L-lysine is also shown in Figure 7. The addition of these amino acids to the feeds saves the use of feed protein without affecting the growth response of animals. L-Tryptophan is the second limiting amino acid of maize and as the feed protein level becomes lower, its requirement increases. When the protein level decreases further, L-threonine becomes another limiting amino acid. In Western Europe where wheat and barley are the basis of feeds, L-threonine is the second limiting amino acid after L-lysine and both are usually added to the feedstuff. The issue most focused on at present is development of protected amino acids for ruminants (220). Protected methionine has already been commercialized.

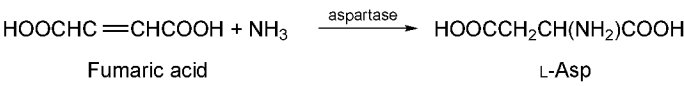
L-Alanine



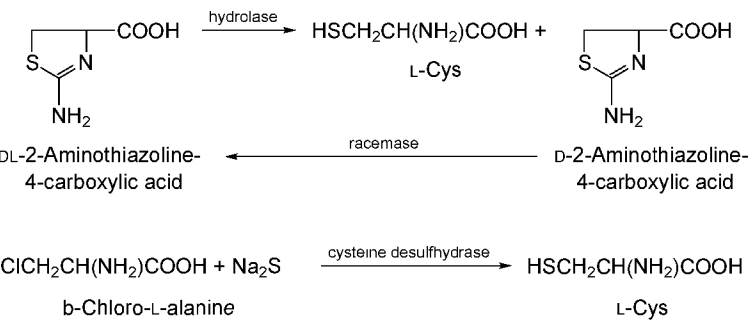
D-Alanine



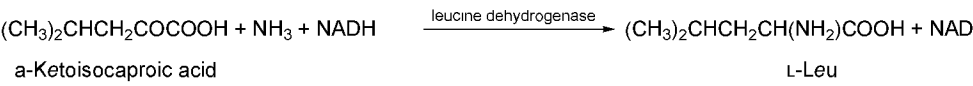
L-Aspartic acid



L-Cysteine



L-Leucine



L-Lysine

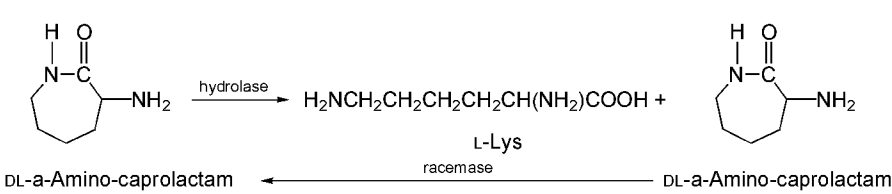
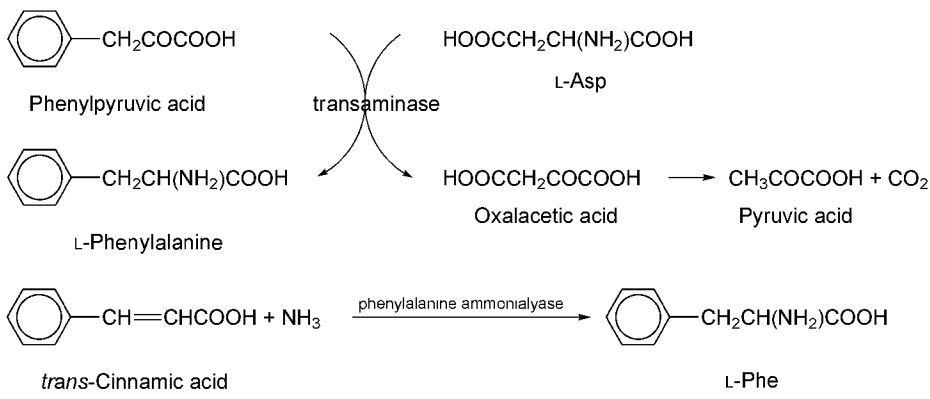
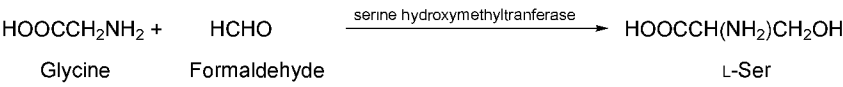


Fig. 6. Representative chemical reactions in the enzymatic production of amino acids.

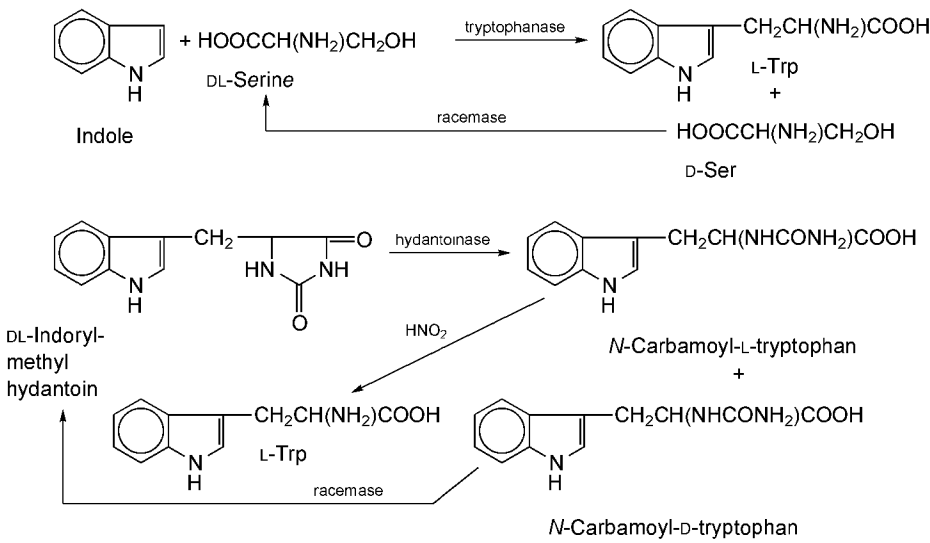
L-Phenylalanine



L-Serine



L-Tryptophan



L-Tyrosine

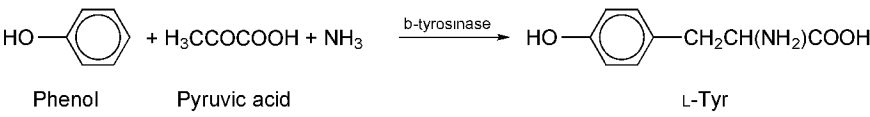


Fig. 6b. Continued

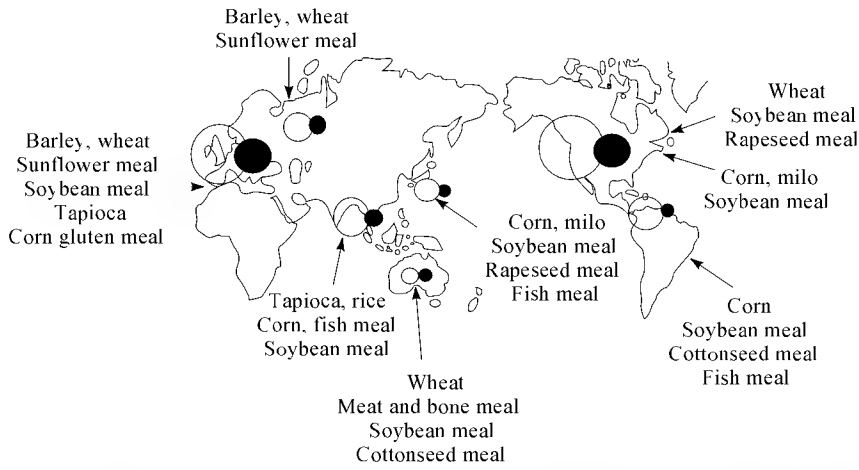


Fig. 7. Feedstuffs and amino acids (176). ○, methionine, 16 × 10⁶ t yr; ●, lysine, 10 × 10⁶ t yr.

Table 12. Limiting Amino Acids of Some Common Feedstuffs for Pig and Chicken^a.

Ingredient	Crude protein, %	Pig		Chicken	
		First	Second	First	Second
maize	8.9	Lys	Trp	Lys	Trp
sorghum	9.5	Lys	Thr	Lys	Arg
barley	11.1	Lys		Lys	Met
wheat	12.6	Lys	Thr	Lys	Thr
soybean meal	46.2	Met	Thr	Met	Thr
fish meal	64.3			Arg	
rapeseed meal	35.3	Met		Lys	Arg
peanut meal	47.4	Lys		Met	Lys
sunflower seed meal	31.7	Lys		Met	Thr
meat and bone meal	48.6	Lys		Trp	Met
cottenseed meal	64.3	Lys	Thr	Lys	Met
corn gluten meal	63.6	Lys	Trp	Lys	Trp

^a Ref. 214

In Foods. Each amino acid has its characteristic taste of sweetness, sourness, saltiness, bitterness, or "umami" as shown in Table 13. Umami taste, which is typically represented by L-glutamic acid salt (and some 5'-nucleotide salts), makes food more palatable and is recognized as a basic taste, independent of the four other classical basic tastes of sweet, sour, salty, and bitter (221).

Table 13. Taste Profiles of L-Amino Acids^a

L-Amino acid	Threshold value, mg/dL	Taste quality ^b				
		Sweet	Sour	Bitter	Salty	Umami
Gly	110	++				
Hyp	50	++		++		
β-Ala	60	++				+
Thr	260	++				
Pro	300	++		+++		
Ser	150	++				+
Lys·HCl	50	++		++		+
Gln	250	+				+
Phe	150			+++		
Trp	90			+++		
Arg	10			+++		
Arg·HCl	30	+		+++		
Ile	90			+++		
Val	150	+		+++		
Leu	380			+++		
Met	30			+++		+
His	20			++		
His·HCl	5		+++	+	+	
Asp	3		+++			+
Glu	5		+++			++
Asn	100		++	+		
MSG	30	+			+	+++
monosodium aspartate	100				++	++

^a Ref. 214.

^b Profiles of each basic taste intensity are expressed as follows: (+++) strongest, (++) stronger, and (+) detectable.

The existence of protein receptors in the tongues of mice and cows have been shown. Monosodium L-glutamate MSG [142-47-2] is utilized as a food flavor enhancer in various seasonings and processed foods. D-Glutamate is tasteless. L-Aspartic acid salt has a weaker taste of umami. Glycine and L-alanine are slightly sweet. The relationship between taste and amino acid structure has been discussed (222).

Aspartame (L-aspartyl-L-phenylalanine methyl ester [22839-47-0]) is about 200 times sweeter than sucrose. The Acceptable Daily Intake (ADI) has been established by JECFA as 40 mg/kg/day. Structure-taste relationship of peptides has been reviewed (223). Demand for L-phenylalanine and L-aspartic acid as the raw materials for the synthesis of aspartame has been increasing. D-Alanine is one component of a sweetener "Alitame" (224).

In traditional cooking of proteinaceous foods, the fundamental difference between Western and Oriental cultures is that the former cooks proteins with unseasoned fats and the latter cooks with many kinds of traditional seasonings that have tastes of amino acids. Western cultures have some traditional foods with amino acid taste such as cheese. Protein hydrolysates are popular as seasonings (225).

The enzymatic hydrolysates of milk casein and soy protein sometimes have a strong bitter taste. The bitter taste is frequently developed by pepsin [9001-75-6], chymotrypsin [9004-07-3], and some neutral proteases and accounted for by the existence of peptides that have a hydrophobic amino acid in the carboxylic terminal (226). The relation between bitter taste and amino acid constitution has been discussed (227).

Amino acids play a role in food processing in the development of a cooked flavor as the result of a chemical reaction called the nonenzymatic browning reaction (228).

Currently available proteins are all deficient to greater or lesser extent in one or more of the essential amino acids. The recently advanced plastein reaction (229) has made it possible to use protein itself as substrate and to attach amino acid esters to the protein with high efficiency. By this method, soy bean protein (which is deficient in methionine) has been improved to the extent of having covalently attached L-methionine at 11%.

In Parenteral and Enteral Nutrition. Amino acid transfusion has been widely used since early times to maintain basic nitrogen metabolism when proteinaceous food cannot be eaten. It was very difficult to prepare a pyrogen-free transfusion from protein hydrolysates. Since the advances in L-amino acid production, the crystalline L-amino acids have been used and the problem of pyrogen in transfusion has been solved. The formulation of amino acid transfusion has been extensively investigated, and a solution or mixture in which the ratio between essential and nonessential amino acid is 1:1, has been widespread clinically. Special amino acid mixtures (eg, branched chain amino acids-enriched solution) have been developed for the treatment of several diseases (93).

In Medicine. Many amino acids have been used or studied for pharmaceutical purposes. L-Glutamine has been used as a remedy for gastric and duodenal ulcers. L-DOPA [L-3-(3,4-dihydroxyphenyl)alanine] has been widely employed as an antiparkinsonism agent. L- α -MethylDOPA is an effective antihypertensive drug. L-Tryptophan and 5-hydroxy-L-tryptophan [4350-09-8] are effective as antidepressants. In animal experiments it was demonstrated that L-tryptophan induces sleep. Potassium aspartate [14007-45-5] is widely used for improving disturbances in electrolyte metabolism. Calcium aspartate [10389-09-0] is known as a calcium supplement. Glutamic acid hydrochloride is a gastric acidifier which acts to counterbalance a deficiency of hydrochloric acid in the gastric juice. L-Arginine and L-ornithine are used for ammonia detoxification. *p*-Hydroxy-D-phenylglycine, D-phenylglycine, D-cysteine (230), D-aspartic acid (231) are important as the side chains of β -lactam antibiotics (see ANTIBIOTICS, β -LACTAMS). D-Homophenylalanine (232) is a raw material for chemical synthesis of enalapril [75847-73-3], an inhibitor of angiotensin converting enzymes. D-Valine (233) is the raw material for the chemical synthesis of pyrethroid agricultural chemicals. For the details of the use of amino acids in medicine, see reference 184.

In Cosmetics. Amino acids and their derivatives occur in skin protein, and they exhibit a controlling or buffering effect of pH variation in skin and a bactericidal effect (216). Serine is one component of skin care cream or lotion. *N*-Acylglutamic acid triethanolamine monosalt is used for shampoo. Glucose glutamate is a moisturizing compound for hair and skin (234).

Cysteine is used as a reductant for cold wave treatment in place of thioglycolic acid. *N*-Lauroylarginine ethyl ester [48076-74-0] is applied as the hydrochloride as a preservative. Urocanic acid [104-98-3] which is derived from histidine is used in skin cream as a uv absorber (235).

In Industrial Chemicals. Recently, as some amino acids (eg, L-glutamic acid, L-lysine, glycine, DL-alanine, DL-methionine) have become less expensive chemical materials, they have been employed in various application fields. Poly(amino acid)s are attracting attention as biodegradable polymers in connection with environmental protection (236).

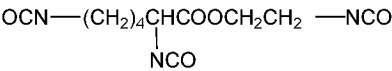
Surfactants. *N*-Acylglutamates, sodium *N*-lauroyl sarcosinate [137-16-6], and *N*-acyl- β -alanine Na salt are used in the cosmetic field as nontoxic surfactants (237). Some of them (eg, *N*-acylglutamic acid dibutylamide) are used as oil gellating agents to recover effluent oil in seas and rivers (238).

Liquid Crystals. Ferroelectric liquid crystals have been applied to LCD (liquid crystal display) because of their quick response (239). Ferroelectric liquid crystals have chiral components in their molecules, some of which are derived from amino acids (240). Concentrated solutions (10–30%) of α -helix poly(amino acid)s show a lyotropic cholesteric liquid crystalline phase, and poly(glutamic acid ester) films display a thermotropic phase (241). Their practical applications have not been determined.

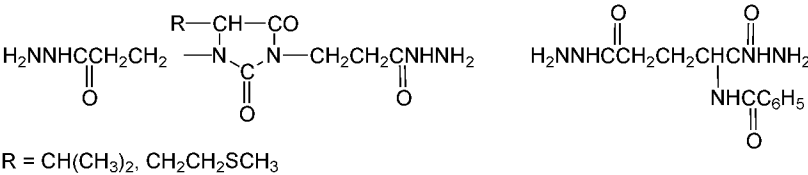
Artificial Leather. Poly(γ -methyl glutamate) [29967-97-3] that has excellent weatherability, nonyellowing, high moisture permeability, and heat resistance, was developed as the original coating agent for artificial leather (85). To improve flexibility and stretch, a block copolymer with polyurethane was developed. Poly(L-leucine) [25248-98-0] is being tested as artificial skin or wound dressing (242).

Protected Amino Acids. Various types of protected amino acids for peptide synthesis are available commercially (243).

Isocyanate. Lysine has two amino groups in the molecule and diisocyanate is prepared by reaction with phosgene. Lysine triisocyanate [69878-18-8] (LTI) is developing on a commercial scale in Japan (244).



Hardeners and Vulcanizing Agents. For epoxy resins, acylhydrazide derivatives of amino acids are used (245).



As vulcanizing agents, amino acids with or without sulfur are used for nipple rubber of babies' bottles and rubbers used in medical applications (246).

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L-MONOSODIUM GLUTAMATE(MSG)

Monosodium glutamate (MSG), more specifically monosodium L-glutamate, is used in large quantities as a flavor enhancer throughout the world. The industrial production of MSG began in Japan in the early 1900s. Its annual production was estimated at more than 350,000 tons in 1988 (1). The world capacity for production of MSG approximates 500,000 tons per year and continues to increase. The demand for MSG is expected to increase in developing countries as its use in commercially prepared, packaged foods, ready made soups, and as a table seasoning increase in Western and Asian countries.

L-Glutamic acid was first isolated in 1886 (2) from the acid hydrolyzate of wheat gluten and thus named Glutaminsäure; its structure was identified chemically in 1890 (3). In 1908 the ability of glutamate to enhance the flavor of foods was discovered (4). This research (4) was based on the hypothesis that besides the usually recognized four taste elements of bitter, sour, salty, and sweet there was another group of taste substances in foods. A kelp-like seaweed harvested around Japan, known as konbu, *Laminaria Japonica*, had been used for many centuries in Japan to improve the flavor of soups and other foods. Kikunae Ikeda isolated the flavor-enhancing part from extracted kelp soup with hot water and identified its taste-enhancing component as sodium glutamate. Immediately he filed a patent application (5) and commercial production of MSG began in Japan in 1909.

Properties

Monosodium L-glutamate [142-47-2], C₅H₈NO₄Na·H₂O (mol wt 187.13) crystallizes from aqueous solution at room temperature as rhombic prisms. Its structure, as determined by x-ray crystallography (6), indicates that the sodium ions are coordinated octahedrally by four (3α and 1γ) carboxyl oxygen atoms and two water molecules as follows:

crystal system: orthorhombic
space group: *P*2₁2₁2₁
z = 8 (2 formula units in the asymmetric unit)
a = 1.5267(9)nm, *b* = 1.7937(9)nm, *c* = 0.5562(4)nm
V = 1.520 nm³, *D_x* = 1.635 g cm⁻³, *D_m* = 1.63 g cm⁻³

Commercially preferred crystals for use as flavor enhancement are obtained by crystallization in the presence of amino acids such as alanine (7). The solubility of MSG may be expressed by the following equation (8):

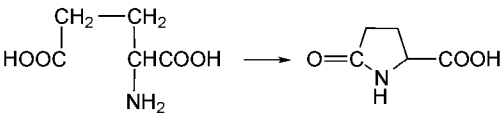
$$S = 35.30 + 0.098t + 0.0012t^2$$

where *S* is % of anhydrous monosodium glutamate in a saturated solution at °C and the remainder at equilibrium is the monohydrate. Below -0.8°C, MSG crystallizes as the pentahydrate (8). The filtered pentahydrate loses its water of crystallization upon exposure to air to become the extremely porous monohydrate (9). A 3% aqueous solution of MSG at 25°C has a pH of 7.

Crystalline MSG is less hygroscopic than sodium chloride. The critical humidities of MSG are 96.0, 94.8, and 90.0 at 20, 30, and 50°C, respectively. MSG loses its water of crystallization at 120°C; intramolecular dehydration occurs at 155°C. The decomposition temperature is 225°C.

The α-carbon of glutamic acid is chiral. A convenient and effective means to determine the chemical purity of MSG is measurement of its specific rotation. The specific optical rotation [α]_D²⁰ of a solution of 10 g MSG in 100 mL of 2 N HCl is +25.16. Besides L-glutamic acid [56-86-0], D-glutamic acid [6893-26-1] and the racemic mixture, DL-glutamic acid [617-65-2], are known. Unique taste modifying characteristics are possessed only by the L-form.

L-Glutamic acid does not racemize in neutral solution, even at 100°C. Deviation of pH from neutral to greater than 8.5 results in thermal racemization with loss of taste characteristics. Racemization in neutral solution occurs at 190°C after formation of the lactam, 5-oxo-L-proline, pyroglutamic acid [98-79-3].



The reaction is very slow in neutral solution, but the equilibrium shifts toward the lactam rather than glutamic acid. Under strongly acidic or alkaline conditions, the ring-opening reaction requires a very short time (10). Therefore, neutralization of L-glutamic acid should be performed cautiously because intramolecular dehydration is noticeable even below 190°C.

Racemization also occurs in the presence of microbial racemase. As for other amino acids, the racemase that is specific for glutamic acid is found in *Lactobacillus fermenti*.

L-Glutamic acid is split into α-ketoglutaric acid [328-50-7] (2-oxo-pentanedioic acid) and ammonia by glutamate dehydrogenase. By the reverse reaction, L-glutamic acid is synthesized from α-ketoglutaric acid, a component of the tricarboxylic acid (TCA) cycle of glycolysis. Whereas glutamate transaminase is nonspecific for the pairs of keto-acids and amino acids, L-glutamic acid is the only amino acid in mammalian tissues that undergoes oxidative deamination at an appreciable rate. The formation of ammonia from α-amino groups of other amino acids requires their conversion to the α-amino nitrogen of L-glutamic acid (11). Thus, L-glutamic acid is a key substance in metabolism of amino acids.

Glutamic acid dehydrogenase is widely distributed in microorganisms and higher plants as a catalyst in the synthesis of L-glutamic acid from α-ketoglutaric acid and free ammonia. Transaminase is contained in a wide variety of microorganisms.

Production

Classical Processes. From 1909, when industrial production of MSG started, until 1965, when the extraction process ended, wheat gluten, separated from wheat flour by washing the starch from the dough, was the main raw material (12). It was used because crude dried gluten (12% as nitrogen) contains as much as 25% L-glutamic acid, the highest content among industrial raw materials. Crude gluten was hydrolyzed by heating with hydrochloric acid. After concentration under reduced pressure, the hydrolyzate was cooled after adding concentrated hydrochloric acid to crystallize L-glutamic acid hydrochloride [138-15-8], L-glutamic acid can be easily separated from other amino acids in the form of its hydrochloride because of its very low solubility in concentrated hydrochloric acid. The hydrolyzate suspends relatively large amounts of humic material formed by the reaction of amino acids and carbohydrates. Filtration and hydrolysis are very troublesome processes in terms of the equipment required and the environment. Several improvements have been made in the crystallization of the hydrochloride; the filtered wet hydrochloride contains less than 30% of L-glutamic acid, not sufficient to warrant its use as a raw material for the manufacture of pure MSG. The crude hydrochloride is dissolved in hot water and filtered again to separate the humic substances formed after the first filtration. The pH of the refined filtrate is adjusted with caustic soda or ammonia to 3.2, the isoelectric point of glutamic acid, to precipitate L-glutamic acid crystals. Since its solubility is less than 1 g/100 mL-water at room temperature (0.86 g per 100 mL at

25°C), the yield of more than 90% purity L-glutamic acid crystals is very high. The glutamic acid crystals appear as both the metastable α - and stable β -forms. The α -form consists of prismatic crystals which are easy to filter, whereas the β -form needle crystals are difficult to filter. Control of crystallization conditions of α -crystals are required (13). The crude L-glutamic acid crystals are suspended in water and neutralized with caustic soda or sodium hydroxide. The solution is decolorized with activated carbon to produce a transparent solution and MSG is crystallized under reduced pressure. The crystals of MSG are then separated from the mother liquor by centrifugation and dried for packaging.

In the United States and some European countries, beet-sugar-waste molasses, or Stefen's waste, has been used as raw material for MSG production. The 2-pyrrolidinone-5-carboxylic acid [98-79-3] contained in beet sugar as by-product, is hydrolyzed at weakly alkaline pH, and moderate temperature (eg, pH 10.5–11.5, at 85°C for 2 h) to avoid racemization (14). The pH of the hydrolyzate is adjusted to 3.2 with a mineral acid to precipitate crystals of L-glutamic acid. The L-glutamic acid crystals obtained are transformed to MSG as described above.

Fermentation Process. In the early 1950s, the excretion of small amounts of amino acids in the culture medium of *Escherichia coli* was reported (15) and it was found that addition of excess ammonium salts resulted in an increase in the accumulation of amino acids in the culture medium. In 1957, a new strain of *Micrococcus glutamicum* (afterwards renamed *Corynebacterium glutamicum*) which accumulates large quantities of L-glutamic acid was discovered (16). This novel method enabled yields of L-glutamic acid of about 30% based on the weight of glucose incubated in its cultivating broth, and was immediately applied for industrial production. This discovery led to the fermentation production of many other amino acids by inducing various artificial mutants (17).

Glutamic acid-producing microorganisms are distributed widely throughout the natural environment. They are classified taxonomically as the *Micrococcus*, *Brevibacterium*, *Corynebacterium*, *Aerobacter* sp. and *Microbacterium* genera. Most of these microorganisms are gram-positive, nonspore-forming, nonmotile, and require biotin [58-85-5] for growth. They all have intense glutamate dehydrogenase activity and oxidative degradability, to both L-glutamic acid and α -ketoglutaric acid.

The carbon sources for biosynthesis of glutamic acid include acetic acid and the commonly used carbohydrates (18). For industrial production, molasses and starch hydrolyzate are generally used at present. In L-glutamic acid fermentation, the accumulation of L-glutamic acid is governed not only by its biosynthesis in the bacterial cells but also by its secretion. Biotin is one of the vitamins essential for cell growth, but a biotin concentration in the culture medium sufficient for cell growth makes the cell membranes impermeable for L-glutamic acid and results in poor accumulation (19). The critical biotin content of the cells for L-glutamic acid production is 0.5×10^{-6} g g-dry cells (20). The limited amount of biotin is believed to cause incomplete biosynthesis of oleic acid [112-80-1], which results in a decrease of the phospholipids in the cell membrane and makes the membrane permeable. If an excessive amount of biotin is added, the result is a dramatic reduction of the L-glutamic acid excreted and accumulation of lactic and α -ketoglutaric acids. This specific function of biotin applies to all microorganisms requiring biotin.

Molasses is useful as a raw material for L-glutamic acid fermentation, except that it requires processing to depress its excess biotin concentration. To reduce this activity, surface active substances ($C_{11}-C_{18}$ saturated fatty acid esters of polyoxyethylene) (21) are added at an early stage of production to retard microorganism propagation. Furthermore, the addition of sugar at a concentration of culture media below approximately 10% is necessary so as not to retard propagation. Additional sugar is fed during fermentation to obtain a higher concentration of excreted L-glutamic acid. This technology made possible a concentration of approximately 80 g/L of L-glutamic acid. Ammonium salts or a solution of urea or gaseous ammonia are convenient nitrogen sources for the fermentation, not only as the initial medium but also to maintain the pH of the culture at 7–8 for microbial growth and product formation. The culture medium becomes acidic because of assimilation of ammonium ions and formation of L-glutamic acid. Gaseous ammonia can be used advantageously to maintain neutral pH and avoid dilution of the culture medium, resulting in the high accumulation of glutamate in the fermentation broth, because it does not contain OH⁻ ions or water.

Microorganisms require several minerals such as ferrous and potassium ions which play important roles in glutamic acid fermentation. Other important culture conditions include regulating aeration stirring. The biosynthesis of L-glutamic acid is performed under regulated aerobic conditions. When oxygen is not sufficiently dissolved, lactic and succinic acids accumulate and reduce accumulation of L-glutamic acid. On the other hand, an excess of dissolved oxygen results in the formation of α -ketoglutaric acid. The need to regulate oxygen transfer led to the development of novel technologies for measuring the rate of oxygen transfer, which include the use of sodium sulfite solution. By using this technique, the optimal oxygen transfer rate was determined (22). The pressure of dissolved oxygen must strictly be kept above 1 kPa (0.01 atm) by aeration and agitation in the industrial fermentor. The air, sterilized by passing through sterile filtration such as glass wool, is fed to the industrial fermentor as well. Carbon dioxide is formed during fermentation and causes the cultivation medium to foam heavily. Mechanical defoaming alone does not provide sufficient control; chemical antifoaming agents and biochemically inert silicone oils are employed as well.

The optimum temperature for fermentation is 30–37°C depending on the microorganisms used. Regulation of the temperature using heat exchangers installed inside of the fermentor is indispensable. Fermentation is an exothermic reaction, and the temperature critically affects not only propagation of microorganisms but also the formation of L-glutamic acid. L-Glutamic acid is synthesized biochemically through the glyoxylate cycle as an oxaloacetate generating system without carbon dioxide fixation, and through phosphoenol pyruvic acid [138-08-9] to form oxaloacetic acid [328-42-7] with carbon dioxide. Several mutants with high phosphoenol pyruvate carboxylase activity (23) or low isocitrate lyase activity (24) have improved productivity of L-glutamic acid and the extent of carbon dioxide fixation.

Progress in fermentation technology has made it possible to raise the accumulation and the yield of L-glutamic acid above 100 g/L and 60% based on the total amount of sugar. Application of genetic engineering techniques for further improvement is also in progress.

An industrial fermentor of capacity up to several hundred kiloliters equipped with aeration and stirring devices, as well as other automatic control systems, is used. The cultures must be sterilized and aseptic air must be used owing to the high sensitivity to bacterial contamination of L-glutamic acid fermentation.

In industry, microorganisms used for L-glutamic acid fermentation are usually preserved under lyophilization, or when stocked for short periods, preserved by keeping below 10°C. To refresh the microorganisms, stocked in either form, they are inoculated on a strip of an agar medium composed of yeast extract and/or polypeptone, sodium chloride, and agar at an optimal temperature for them. The refreshed microorganisms are then cultivated in a liquid medium in a flask with a sterilized stopper and shaken vigorously. Then they are transferred into a small fermentor to let them propagate to appropriate volume for seed culture. Fermentation takes about 35–40 hours. In the initial stage of fermentation, the propagation of microorganisms is solely observed, but in the middle stage, accumulation of L-glutamic acid emerges. The end of the process is determined by an increase in pH in the medium whereupon the increase in concentration of L-glutamic acid ceases.

Sterilized fermentation broth, either in the fermentor or through a heat exchanger with steam, is transferred to another vessel and then centrifuged to remove the microorganisms and other insoluble organic substances. After the clarified broth has been concentrated under reduced pressure, the pH of the broth is adjusted to 3.2 using hydrochloric or sulfuric acid to recover L-glutamic acid crystals in the α -form. These crude L-glutamic acid crystals are converted to MSG through decolorization and crystallization processes as discussed previously.

Uses

Monosodium L-glutamate elicits a unique taste, known as "umami", which is different from the four basic tastes of sweet, salty, sour, and bitter. Multidimensional graphs of sensory tests show that taste similarity scores of MSG, and of meat, fish, and vegetable stocks which are naturally high in glutamate, fall outside the spaces characterized by the four basic tastes. This suggests that glutamate is not simply a mixture of the four basic tastes, but is an independent basic taste. This concept also comes from studies in physiology, electrophysiology, biochemistry, food chemistry, and nutrition, and basic research on taste receptors (25). A synergistic effect occurs between glutamate and nucleotides such as 5'-inosinic acid [131-99-7] and 5'-guanylic acid [85-32-5] found in meat, fish, vegetables, and mushrooms. Through this effect, even a small addition of glutamate to a food containing the nucleotides remarkably enhances "umami" seven to eight times as much as the original "umami" of the food (26). The taste threshold of MSG is around 0.03% in aqueous solution.

The intensity of "umami" increases linearly with a logarithmic increase in the concentration of MSG. The synergistic effect of MSG with 5'-ribonucleotides is expressed by the following relation

$$y = u + Auv$$

where u and v are the respective concentrations of MSG and 5'-ribonucleotides. A is a constant: 1200 for disodium 5'-inosinate(IMP) and 2800 for disodium 5'-guanylate(GMP), and y is the equivalent concentration of MSG alone. In some commercial "umami" seasonings, 5'-ribonucleotide is added to take advantage of the synergistic effect with MSG (27).

L-Glutamic acid is used as a neutralizing agent for basic compounds, for example, arginine glutamate [4320-30-3] is employed as a pharmaceutical and raw material for cosmetics. Glutamic acid hydrochloride is proposed as an acidifying agent in the stomach. As an amphoteric electrolyte it may be applied as a chelating agent or a builder for a detergents. Sodium pyroglutamate [28874-57-3] obtained by dehydration of L-glutamic acid with heating and then neutralization by sodium oxide is used as a component of a natural moisturizing factor for human skin because of its hygroscopic property (28).

Safety

Monosodium L-glutamate is metabolized in the same way as glutamic acid coming from any digested protein. After oral ingestion, glutamate is absorbed from the intestine by an active transport system. During this process, a large proportion is metabolized to alanine and α -ketoglutarate, which enters the tricarboxylic acid cycle. Glutamate is further metabolized in the liver to give glucose, lactate, glutamine, and other amino acids. Consequently, blood glutamate levels do not rise significantly unless very large doses are administered. Blood glutamate levels rise transiently when large doses are ingested on their own, but the co-ingestion of foods that contain metabolizable carbohydrate increases the metabolism of MSG and eliminates or greatly attenuates this rise. Human infants, including premature infants, metabolize glutamate similarly to adults (29,30).

The acute toxicity of MSG is low (31); the oral LD₅₀ for humans, calculated on the basis of doses administered in different ways to various animals, would represent a single dose greater than 1 kg for a person weighing 70 kg. In contrast, the oral LD₅₀ for sodium chloride in rats is 3.75 g/kg body weight (32).

The main use of MSG is as a food ingredient, and so its safety when used in the diet is the most important aspect of its safety for use. Both short term and chronic toxicity studies on MSG in the diet of several species at doses of up to 4% (approximately 6–8 g/kg body weight per day) in the diet showed no specific toxic effects, and no evidence for carcinogenicity or mutagenicity. Reproduction studies of up to three generations did not reveal any adverse effects of dietary MSG ingestion. Fertility, gestation, viability, and lactation indexes or the pre and post weaning performance of offspring were unaffected. In primates, it was found that the placenta serves as an effective barrier to the transfer of glutamate from the mother to the fetus. The glutamate level of human milk is hardly affected by the oral ingestion of large doses of MSG.

The demonstration that injected or force-fed neonatal rodents given extremely high doses of MSG showed evidence of brain lesions, has led to much additional research to determine any possible link between neurotoxicity and human use of MSG (33). However, no evidence from animal tests indicates that MSG in the diet causes brain damage in humans (34).

Numerous experiments on rodents, as well as dogs and monkeys, with dosage levels up to 43 g of MSG per kilogram of body weight have failed to show any link between dietary use of MSG and brain damage. In the case of dogs and monkeys, even experiments involving injection of MSG have not shown any effects on the brain.

An anecdotal report in 1968 triggered interest in Chinese Restaurant Syndrome (CRS) a reaction associated with transient subjective symptoms of burning, numbness, and a tight sensation in the upper part of the body. Possible association with food ingredients such as MSG was suggested. No objective changes in skin temperature, heart rate, ECG, or muscle tone were observed, and no correlation was seen between plasma glutamate levels and symptoms. In 1979 a survey by questionnaires of more than 3000 people in the United States was conducted. Only 1.8% of those surveyed acknowledged that they experienced possible CRS feelings (35). Only 0.19% of those with symptoms attributed them to eating in Chinese restaurants. These feelings were also found to occur after consumption of spicy tomato juice, orange juice, coffee, and tea. In 1986, self-identified MSG responders were challenged in a properly controlled double-blind study, and it was concluded that the link between MSG and CRS was not supportable (36). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded in 1987 that properly-conducted double-blind studies among individuals who claimed to suffer from the syndrome did not confirm MSG as the causal agent (30). JECFA is a scientific advisory body to the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations.

In 1981, Chinese Restaurant Asthma was reported following capsule administration of MSG to several asthmatics (37). However, the researchers failed to account for other allergens to which the subjects could have been exposed and did not utilize the scientific practice of a "control" substance which would have helped to determine if glutamate triggered this response. In a double-blind crossover study, chronic asthmatics were challenged with MSG or a placebo. No decrease in pulmonary function was observed (39).

JECFA reviewed the safety studies of glutamate and endorsed its safety by allocating an Acceptable Daily Intake (ADI) for L-glutamic acid and its monosodium, potassium, ammonium, calcium, and magnesium salts as being "not specified." The scientific committee for food of EC concurred (40).

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AMINO ALCOHOLS.

See ALKANOLAMINES.

AMINOGLYCOSIDES (AMINOCYCLITOL).

See ANTIBIOTICS—AMINOGLYCOSIDES.

AMINOLYSIS.

See AMMONIA.

AMINONAPHTHALENES.

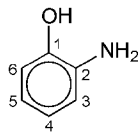
See NAPHTHALENE DERIVATIVES.

AMINONAPHTHOLS.

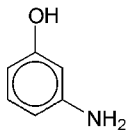
See NAPHTHALENE DERIVATIVES.

AMINOPHENOLS

Aminophenols and their derivatives are of commercial importance, both in their own right and as intermediates in the photographic, pharmaceutical, and chemical dye industries. They are amphoteric and can behave either as weak acids or weak bases, but the basic character usually predominates. 3-Aminophenol (2) is fairly stable in air unlike 2-aminophenol (1) and 4-aminophenol (3) which easily undergo oxidation to colored products. The former are generally converted to their acid salts, whereas 4-aminophenol is usually formulated with low concentrations of antioxidants which act as inhibitors against undesired oxidation.



(1)



(2)



(3)

Physical Properties

The simple aminophenols exist in three isomeric forms depending upon the relative positions of the amino and hydroxyl groups around the benzene ring. At room temperature they are solid crystalline compounds. In the past the commercial-grade materials were usually impure and colored because of contamination with oxidation products, but now virtually colorless, high purity commercial grades are available. The partitioning of aminophenols between aqueous and organic solvent systems has been studied; 2-aminophenol behaves anomalously because of intramolecular hydrogen bonding (1,2). The solubilities of these compounds in common solvents of differing polarities (dielectric constants) are given in Table 1 and their spectral characteristics in

Table 2. In acidic solution all isomers exhibit fluorescence. 4-Aminophenol shows two bands; one at 300 nm common to all the isomers, and the second at 370 nm attributed to the existence of an additional aqueous ionic species. Fluorescence also exists in neutral solution, but is abolished at high pH values (3–13).

Table 1. Solubility^a of Aminophenols in Common Solvents Arranged in Order of Increasing Polarity (Dielectric Constant)^b

Solvent	2-Aminophenol	3-Aminophenol	4-Aminophenol
benzene	1	1	0
toluene	1	1	1
acetonitrile	3	3	2
diethyl ether	2	3	1
chloroform	1	1	0
ethyl acetate	3	3	2
acetone	3	3	2
ethanol	2	3	1
dimethyl sulfoxide	3	3	3
water			
hot	2	3	2
cold	1	2	1

^a 0, insoluble; 1, slightly soluble; 2, soluble; 3, very soluble.

^b Eluotropic series.

Table 2. Spectral Characteristics of the Aminophenol Isomers

	2-Aminophenol	3-Aminophenol	4-Aminophenol
uv ^a nm			
absorption			
	233,285 (methanol)	287 (methanol)	234,301 (methanol)
	229,281 (water)	270 (0.1 M HCl)	229,294 (water)
	235,288 (cyclohexane)	234,284 (cyclohexane)	235,304 (cyclohexane)
emission	λ_{cx} λ_{em}	λ_{cx} λ_{em}	λ_{cx} λ_{em}
fluorescence	291 336 (ethanol)	287 333 (ethanol)	302 364.5 (ethanol)
	286 338–344 (water)	286 331–334 (water)	301 367–374 (water)
	283 330 (cyclohexane)	290 320 (cyclohexane)	270 330 (cyclohexane)
phosphorescence	291 440 (ethanol)	287 425 (ethanol)	302 470 (ethanol)
ir ^b cm ^{−1}	3380,3300,1600,1510,1470,1270,900,740	3370,3310,1600,1470,1390,1260,1180,910	3050–2580,1500,1470,1240,970,830,750
ms ^c	109 (100)	109 (100)	109 (100)
	80 (39)	80 (23)	80 (31)
	53 (12)	81 (10)	107 (23)
	28 (11)	53 (6)	53 (20)
nmr ^d ppm	6.9–7.5,8.6 (TFA)	4.7,6.0,6.1,6.8,8.8 (DMSO)	7.1,7.4,8.7 (TFA)

^a Uv spectra: λ_{cx} , excitatory wavelength; λ_{em} , emission wavelength (3,4,7–9).

^b Only ir absorption bands reported as very strong are included (accuracy ± 10 cm^{−1}) (5,6).

^c Values quoted are ion (m/z) followed by relative abundance in parentheses. After m/z 109 and 80, the other ions may vary in abundance order dependent upon conditions employed (10).

^d Proton chemical shift spectra over the range of 0–15 ppm (± 0.1 ppm): TFA, trifluoroacetic acid; DMSO, dimethyl sulfoxide. When complex spectra caused by second-order effects or overlapping resonances were encountered, the range was record (11,12).

2-Aminophenol. This compound forms white orthorhombic bipyramidal needles when crystallized from water or benzene, which readily become yellow-brown on exposure to air and light. The crystals have eight molecules to the elementary cell and a density of 1.328 g cm^{−3} (1.29 also quoted) (14–16). The molecules are hydrogen bonded from OH to N to form chains parallel to the b-axis; these chains are linked together to form sheets by NH-to-O hydrogen bonds essentially parallel to the c-axis. There are large cavities between the sheets permitting the intercalation of small foreign molecules (17) (see Tables 3–5).

Table 3. General Properties of Aminophenols

Property	2-Aminophenol	3-Aminophenol	4-Aminophenol
alternative names	2-hydroxyaniline 2-amino-1-hydroxybenzene	3-hydroxyaniline 3-amino-1-hydroxybenzene	4-hydroxyaniline 4-hydroxy-1-aminobenzene
C.I. designation	76,520		
CAS Registry Number	[95-55-6]	[591-27-5]	[123-30-8]
molecular formula	C ₆ H ₇ NO	C ₆ H ₇ NO	C ₆ H ₇ NO
molecular weight	109.13	109.13	109.13
melting point, °C	174	122–123	189–190 ^a
boiling point, °C			
0.04 kPa			130 ^a , 110 ^b
0.4 kPa			150
1.07 kPa			167
1.47 kPa	153 ^{b,c}	164 ^c	174
101.3 kPa			284
ΔH_f , kJ mol ^{−1}	191.0 $\pm$ 0.9	194.1 $\pm$ 1.0	190.6 $\pm$ 0.9 ^e

^a Decomposes.
^b Sublimes. To convert kPa to mm Hg, multiply by 7.5.
^c Ref. 18.
^d In the crystalline state (19). To convert kJ to kcal, divide by 4.184.
^e 179.1 is also quoted (20).

Table 4. Acid Dissociation Constants ^a of Aminophenols ^b

Compound	p <i>K</i> ₁	p <i>K</i> ₂	Temperature, °C
2-aminophenol	4.72		21
	4.66 ^c		25
		9.66	15
		9.71	22
3-aminophenol	4.17		21
	4.31 ^c		25
		9.87	22
4-aminophenol	5.5		21
	4.86	10.60	30
	5.48 ^c		25
		10.30	22

^a In water unless otherwise noted.
^b Refs. 21, 22, and 23.
^c 1 vol % ethyl alcohol in water.

Table 5. Salts of the Aminophenols

Salt	2-Aminophenol	3-Aminophenol	4-Aminophenol
hydrochloride			
CAS Registry Number	[51-19-4]	[51-81-0]	[51-78-5]
melting point, °C	207	224	306 ^a
crystal form	needles	prisms	prisms
hydroiodide			
CAS Registry Number			[33576-76-0]
melting point, °C		209	
crystal form		prisms	
oxalate			
melting point, °C	167.5 ^a	275	183
acetate			
CAS Registry Number	[97777-54-3]	[97777-55-4]	[13871-68-6]
melting point, °C	150 ^b		183
chloroacetate			
melting point, °C			148
crystal form			needles
trichloroacetate			
CAS Registry Number	[97777-57-6]	[97777-56-5]	
melting point, °C			166
crystal form			needles
sulfate			
CAS Registry Number		[66671-80-5]	[54646-39-8]
melting point, °C		152	
crystal form		plates or needles	
hydrosulfate			
CAS Registry Number	[40712-56-9]		[15658-52-3]
melting point, °C			272
crystal form			needles

^a Decomposes.
^b The formate salt melts at 120°C.

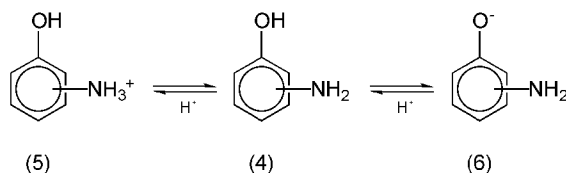
3-Aminophenol. This is the most stable of the isomers under atmospheric conditions. It forms white prisms when crystallized from water or toluene. The orthorhombic crystals have a tetramolecular unit and a density of 1.195 g cm³ (1.206 and 1.269 also quoted) (15,16) (see Tables 3–5).

4-Aminophenol. This compound forms white plates when crystallized from water. The base is difficult to maintain in the free state and deteriorates rapidly under the influence of air to pink-purple oxidation products. The crystals exist in two forms. The α-form (from alcohol, water, or ethyl acetate) is the more stable and has an orthorhombic pyramidal structure containing four molecules per unit cell. It has a density of 1.290 g cm³ (1.305 also quoted). The less stable β-form (from acetone) exists as acicular crystals that turn into the α-form on standing; they are orthorhombic bipyramidal or pyramidal and have a hexamolecular unit (15,16,24) (see Tables 3–5).

Chemical Properties

The chemical properties and reactions of the aminophenols and their derivatives are to be found in detail in many standard chemical texts (25). The acidity of the hydroxyl function is depressed by the presence of an amino group on the benzene ring; this phenomenon is most pronounced with 4-aminophenol.

The amino group behaves as a weak base, giving salts with both mineral and organic acids. The aminophenols are true ampholytes, with no zwitterion structure; hence they exist either as neutral molecules (4), or as ammonium cations (5), or phenolate ions (6), depending on the pH value of the solution.



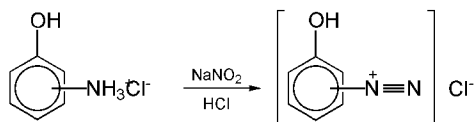
The existence of half-salt complex cations $B^+_{\frac{1}{2}}$, formed by the association of an ammonium cation B^+ , with a neutral molecule, B, has also been postulated. This association phenomenon is most apparent with 4-aminophenol, but is also displayed by the other isomers (23).

The aminophenols are chemically reactive, undergoing reactions involving both the aromatic amino group and the phenolic hydroxyl moiety, as well as substitution on the benzene ring. Oxidation leads to the formation of highly colored polymeric quinoid structures. 2-Aminophenol undergoes a variety of cyclization reactions.

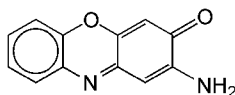
Alkylation. All the possible mono-, di-, and trimethylated aminophenols are known. *N*-Monoalkylation occurs when the aminophenol is heated with the appropriate alkyl halide or with an alcohol and Raney nickel; equal or even better results can be achieved using aldehydes or ketones in place of the alcohol. Specific alkylation of the hydroxyl group to form methoxyanilines (anisidines) or ethoxyanilines (phenetidines) is difficult because of the reactivity of the amino group; mixed alkylated products usually are obtained. 3-Methoxyanilines may be prepared by methylation of 3-aminophenol under alkaline conditions, but it is more usual to protect the amino group and to methylate 3-acetylaminophenol, followed by hydrolysis. The other anisidines and phenetidines are prepared indirectly by reduction of the nitro analogue.

Acylation. Reaction conditions employed to acylate an aminophenol (using acetic anhydride in alkali or pyridine, acetyl chloride and pyridine in toluene, or ketene in ethanol) usually lead to involvement of the amino function. If an excess of reagent is used, however, especially with 2-aminophenol, *O,N*-diacylated products are formed. Aminophenol carboxylates (*O*-acylated aminophenols) normally are prepared by the reduction of the corresponding nitrophenyl carboxylates, which is of particular importance with the 4-aminophenol derivatives. A migration of the acyl group from the O to the N position is known to occur for some 2- and 4-aminophenol acylated products. Whereas ethyl 4-aminophenyl carbonate is relatively stable in dilute acid, the 2-derivative has been shown to rearrange slowly to give ethyl 2-hydroxyphenyl carbamate [35580-89-3] (26).

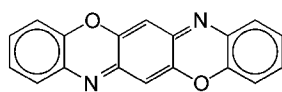
Diazonium Salt Formation. The aromatic amino group of aminophenols can be converted to the diazonium salt using sodium nitrite in aqueous acid, although difficulties may be encountered when the aminophenol is of low solubility or easily oxidized. Crystalline diazonium salts have been isolated using the hydrochloride or sulfate of the appropriate aminophenol under anhydrous conditions. Such diazo derivatives find extensive use in the dye industry (27,28).



Cyclization Reactions. 2-Aminophenol is particularly susceptible to cyclization and condensation reactions because of the close proximity of the amino and hydroxyl groups attached to the benzene ring. A nonspecific oxidative environment (ferric chloride, light, enzymes, autooxidation on silica thin-layer plates) gives 2-aminophenoxazin-3-one [1916-59-2] (7), further oxidation (ferric cyanide, heating in ethanolic potassium hydroxide) gives a pentacyclic structure, triphenoxindioxazine (benzoxazinophenoxazine) [258-72-0] (8). 2-Aminophenol and its derivatives are useful starting materials for the synthesis of phenoxazines, phenoxazones, benzoxazoles, and thiobenzoxazoles. Most of these condensation reactions involve heating at 200–300°C with a suitable catalyst (25).



(7)



(8)

Condensation Reactions. Condensation of substituted benzaldehydes with 2-aminophenol in the presence of a catalyst (aluminum, iron, zinc or phosphorus chlorides) yields a Schiff base, with the elimination of water, in 52–88% yields (29). In general, substituted diphenylamines or diphenyl ethers are obtained from aminophenols and suitable reactants by elimination of ammonia or hydrogen chloride.

Reactions of the Benzene Ring. Both the amino and hydroxyl groups attached to the benzene nucleus are electron-donating because of resonance effects, which predominate over electron-withdrawing inductive effects. Many substituted derivatives are known. The controlled interaction of aminophenols with chlorine or bromine in glacial acetic acid can give a variety of mono-, di-, tri-, or tetrahalogenated products. The use of concentrated sulfuric acid or oleum, with or without heat, gives aromatic sulfonic acids. The sulfonic acid group enters the 2- or 4-position relative to the hydroxyl group. Further treatment with oleum leads to the formation of disulfonated compounds. The carboxylation of 3-aminophenol leads to the formation of 4-aminosalicylic acid.

Manufacture and Processing

Aminophenols are either made by reduction of nitrophenols or by substitution. Reduction is accomplished with iron or hydrogen in the presence of a catalyst. Catalytic reduction is the method of choice for the production of 2- and 4-aminophenol (see AMINES BY REDUCTION). Electrolytic reduction is also under industrial consideration and substitution reactions provide the major source of 3-aminophenol.

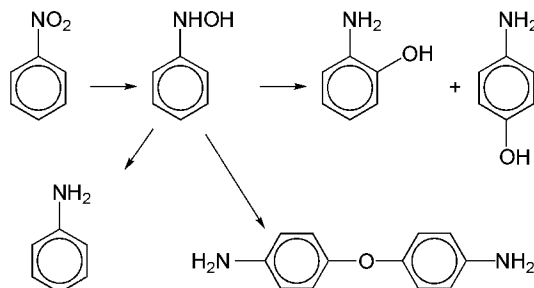
REDUCTION

Iron Reduction. The reduction of nitrophenols with iron filings or turnings takes place in weakly acidic solution or suspension (30). The aminophenol formed is converted to the water soluble sodium aminophenolate by adding sodium hydroxide before the iron-iron oxide sludge is separated from the reaction mixture (31). Adjustment of the solution pH leads to the precipitation of aminophenols, a procedure performed in the absence of air because the salts are very susceptible to oxidation in aqueous solution.

Insoluble red lakes are formed as by-products which decrease yields when 2-nitrophenol [88-75-5] is reduced with iron. Consequently, the iron reduction of this nitro compound to 2-aminophenol is of minor industrial importance today.

Catalytic Reduction. Catalytic reduction usually takes place in solution, emulsion, or suspension in autoclaves or pressurized vessels; after the catalyst is added, the vessel is pressurized with hydrogen (32,33). Water and methanol are the preferred solvents. In water the addition of alkali hydroxide (34), alkali carbonate (35), or acid (36) has been recommended.

The chemical production of aminophenols via the reduction of nitrobenzene occurs in two stages. Nitrobenzene [98-95-3] is first selectively reduced with hydrogen in the presence of Raney copper to phenylhydroxylamine in an organic solvent such as 2-propanol (37). With the addition of dilute sulfuric acid, nucleophilic attack by water on the aromatic ring of *N*-phenylhydroxylamine [100-65-2] takes place to form 2- and 4-aminophenol. The by-product, 4,4'-diaminodiphenyl ether [13174-32-8], presumably arises in a similar manner from attack on the ring by a molecule of 4-aminophenol (38,39). Aniline [62-53-3] is produced via further reduction (40,41).



In past years, metals in dilute sulfuric acid were used to produce the nascent hydrogen reductant (42). Today, the reducing agent is hydrogen in the presence of a catalyst. Nickel, preferably Raney nickel (34), chromium or molybdenum promoted nickel (43), or supported precious metals such as platinum or palladium (35,44) on activated carbon, or the oxides of these metals (36,45), are used as catalysts. Other catalysts have been suggested such as molybdenum and platinum sulfide (46,47), or a platinum–ruthenium mixture (48).

The addition of "wetting agents" increases the aminophenol yield. These agents must be water soluble and stable in the presence of sulfuric acid (49). Quaternary ammonium salts that contain at least one alkyl group with at least ten carbon atoms are suitable (49,50). Dimethylalkylamine oxide increases the hydrogenation rate and improves the selectivity of the reaction for 4-aminophenol (51). The reaction temperature does not usually exceed 100–110°C, and is performed either at atmospheric or at a higher pressure, preferably around 2 MPa (20 atm) (up to 6 MPa). Hydrogen is added during the reaction as it is consumed. The addition of an inert organic solvent, not miscible with water, further increases the yield of 4-aminophenol and product quality (34,35), and the presence of an organic divalent sulfur compound inhibits the formation of aniline (40,41,52).

In another process variant, only 88% of the nitrobenzene is reduced, and the reaction mixture then consists of two phases; the precious metal catalyst (palladium on activated carbon) remains in the unreacted nitrobenzene phase. Therefore, phase separation is sufficient as work-up, and the nitrobenzene phase can be recycled directly to the next batch. The aqueous sulfuric acid phase contains 4-aminophenol and by-product aniline. After neutralization, the aniline is stripped, and the aminophenol is obtained by crystallization after the aqueous phase is purified with activated carbon (53).

Electrolytic Reduction. Electrochemical reduction is finding commercial favor and causes less concern over pollution than metal–acid reduction systems (42,54–56). Electrolysis of nitrobenzene, phenylhydroxylamine, or azoxybenzene [495-48-7] in deoxygenated acid solutions, using graphite or copper–mercury cathodes at potential differences of 300 to 600 mV and temperatures of 60–90°C, produces 4-aminophenol in yields of 65–99% (57,58). Aniline is produced as a by-product (59). The use of 2-nitrophenol yields 2-aminophenol (60); the process does not appear satisfactory for the production of 3-aminophenol (61). The use of bismuth, tin, or titanium salts as additives (62), electrolyte agitation (63), flow-through cells with rotating copper–amalgamated electrodes, and square-wave pulsed current control are increasing the efficiency, product selectivity, and scale up of the process (64,65). Electrocatalytic oxidation of aniline to 4-aminophenol by electrochemically activated molecular oxygen via direct electron transfer from the cathode, in the presence of iron compounds, is also possible (66).

SUBSTITUTION

Substitution of various groups by amino or hydroxyl functions is industrially unimportant for the production of 2- and 4-aminophenol, but this type of reaction is used for the synthesis of 2- and 4-aminophenol derivatives. However, 3-aminophenol cannot be obtained easily by reduction. It is made by the reaction of 3-aminobenzenesulfonic acid [121-47-1] with sodium hydroxide under fusion conditions (5–6 h; 240–245°C). The product is purified by vacuum distillation (25).

In an alternative industrial process, resorcinol [108-46-3] is autoclaved with ammonia for 2–6 h at 200–230°C under a pressurized nitrogen atmosphere, 2.2–3.5 MPa (22–35 atm). Diammonium phosphate, ammonium molybdate, ammonium sulfite, or arsenic pentoxide may be used as a catalyst to give yields of 60–94% with 85–90% selectivity for 3-aminophenol (67,68). A vapor-phase system operating at 320°C using a silicon dioxide catalyst impregnated with gallium sesquioxide gives a 26–31% conversion of resorcinol with a 96–99% selectivity for 3-aminophenol (69).

The direct conversion of aniline into aminophenols may be achieved by hydrogen peroxide hydroxylation in SbF₅–HF at 20 to 40°C. The reaction yields all possible aminophenols via the action of H₂O₂ on the anilinium ions; the major product is 3-aminophenol (64% yield) (70,71). This isomer may also be made by the hydrolysis of 3-aminoaniline [108-45-2] in dilute acid at 190°C (72). Another method of limited importance, but useful in the synthesis of derivatives, is the dehydrogenation of aminocyclohexenones (73).

PURIFICATION

Contaminants and by-products which are usually present in 2- and 4-aminophenol made by catalytic reduction can be reduced or even removed completely by a variety of procedures. These include treatment with 2-propanol (74), with aliphatic, cycloaliphatic, or aromatic ketones (75), with aromatic amines (76), with toluene or low mass alkyl acetates (77), or with phosphoric acid, hydroxyacetic acid, hydroxypropionic acid, or citric acid (78). In addition, purity may be enhanced by extraction with methylene chloride, chloroform (79), or nitrobenzene (80).

Another method employed is the treatment of aqueous solutions of aminophenols with activated carbon (81,82). During this procedure, sodium sulfite, sodium dithionite, or disodium ethylenediaminetetraacetate (82) is added to increase the quality and stability of the products and to chelate heavy-metal ions that would catalyze oxidation. Addition of sodium dithionite, hydrazine (82), or sodium hydrosulfite (83) also is recommended during precipitation or crystallization of aminophenols.

Generally, aminophenols of high purity may be obtained by sublimation at reduced pressure. 3-Aminophenol may be purified by vacuum distillation and a colorless product obtained by adding sulfur dioxide during the distillation (84) or by collecting the distillate under a blanket of unreactive liquid of lower density such as water (85). During shipment contact with metal surfaces should be avoided as they promote oxidation. Transport of the technical grade material usually occurs in heavy duty, plastic-lined paper sacks. The fine chemicals are usually shipped in smaller quantities in brown, air-tight glass bottles.

Economic Aspects

Production figures for the aminophenols are scarce, the compounds usually being classified along with many other aniline derivatives (86). Most production of the technical grade materials (95% purity) occurs on-site as they are chiefly used as intermediate reactants in continuous chemical syntheses. World production of the fine chemicals (99% purity) is probably no more than a few hundred metric tons yearly, at prices of about \$45 per kg in 1990.

Analytical and Test Methods, Storage

Aminophenols have been detected in waste water by investigating uv absorptions at 220, 254, and 275 nm (87). These compounds can also be detected spectrophotometrically after derivatization at concentrations of 1 part per 100 million by reaction in acid solution with *N*-(1-naphthyl)ethylenediamine [551-09-7] (88) or 4-(dimethylamino)benzaldehyde [100-10-7] (89), and the Schiff base formed can be stabilized in chloroform by chelation to increase detection limits (90).

Reaction with 1,3-benzenediamine-periodate (91) or with a hypochlorite–alkaline phenol (Berthelot) reagent enables the detection of both 2- and 4-aminophenol, the latter reagent giving distinguishable blue and dark green products, respectively (92). 4-Aminophenol itself has been shown to react in alkaline solution with both the 2- and 3-aminophenol isomers, a reaction exploited for their detection (93).

More specifically, 2-aminophenol can be detected in solution using an iron(II) sulfate–hydrogen peroxide reagent (94). 3-Aminophenol has been analyzed colorimetrically by oxidation in base and subsequent extraction of a violet quinoneimide dye (95). A colorimetric method using 3-cyano-*N*-methoxypyridinium perchlorate as reagent detects 4-aminophenol in the presence of *N*-acetyl-4-aminophenol (96). 4-Aminophenol has also been detected spectrophotometrically after conversion to indophenol [500-85-6] with alkaline phenol, a method quoted as detecting as little as 10^{-18} mol L (97), and fluorimetrically after reaction with 3-amino-2(1*H*)-quinolinethione to give a yellow-green fluorescent product (98).

Filter paper impregnated with dicarbonyl(benz-2,1,3-thiadiazole)rhodium chloride gives characteristic colorations with the aminophenol isomers after fixation and can be used as an indicator paper (99).

The potentiometric microdetection of all aminophenol isomers can be done by titration in two-phase chloroform-water medium (100), or by reaction with iodates or periodates, and the back-titration of excess unreacted compound using a silver amalgam and SCE electrode combination (101). Microamounts of 2-aminophenol can be detected by potentiometric titration with cupric ions using a copper-ion-selective electrode; the 3- and 4-aminophenol isomers could not be detected by this method (102). Polarographic detection of 4-aminophenol is possible after conversion to the diazonium salt with sodium nitrite (103) and this isomer can also be analyzed by voltametry (104).

Chromatographic methods for the separation, identification, and quantification of aminophenols also have been described (105). Thin-layer chromatography provides a rapid and convenient method of separating the isomers from many derivatives, and subsequent spraying with a variety of chromogenic reagents gives additional information (106,107). Impregnation of plates with nitrite (108) or the use of high performance plates and subsequent densitometry (109) provide quantitation to the level of 0.1 µg.

Several gas-liquid chromatographic procedures, using electron-capture detectors after suitable derivatization of the aminophenol isomers, have been cited for the determination of impurities within products and their detection within environmental and wastewater samples (110,111). Modern high pressure liquid chromatographic separation techniques employing fluorescence (112) and electrochemical (113) detectors in the 0.01 µg range have been described and should meet the needs of most analytical problems (114,115).

Under atmospheric conditions, 3-aminophenol is the most stable of the three isomers. Both 2- and 4-aminophenol are unstable; they darken on exposure to air and light and should be stored in brown glass containers, preferably in an atmosphere of nitrogen. The use of activated iron oxide in a separate cellophane bag inside the storage container (116), or the addition of stannous chloride (117), or sodium bisulfite (118) inhibits the discoloration of aminophenols. The salts, especially the hydrochlorides, are more resistant to oxidation and should be used where possible.

Health and Safety Factors

In general, aminophenols are irritants. Their toxic hazard rating is slight to moderate and their acute oral toxicities in the rat (LD₅₀) are quoted as 1.3 g kg, 1.0 g kg, and 0.375 g kg body weight for the 2-, 3- and 4-isomer, respectively (119). Repeated contamination may cause general itching, skin sensitization, dermatitis, and allergic reactions. Immunogenic conjugates are spontaneously produced upon exposure to 2- and 4-aminophenol (120). Methemoglobin formation with subsequent cyanosis is another possible complication. Inhalation of aminophenols causes irritation of the mucosal membranes and may precipitate allergic bronchial asthma. Thermal decomposition will release toxic fumes of carbon monoxide and nitrogen oxides.

4-Aminophenol is a selective nephrotoxic agent and interrupts proximal tubular function (121,122). Disagreement exists concerning the nephrotoxicity of the other isomers although they are not as potent as 4-aminophenol (123,124). Respiration, oxidative phosphorylation, and ATPase activity are inhibited in rat kidney mitochondria (125). The aminophenols and their derivatives are inhibitors of 5-lipoxygenase (126) and prostaglandin synthetase (127) and are being investigated as therapeutic and prophylactic agents for leukotriene or prostaglandin-induced allergic bronchial, tracheal, and lung disease (128).

Teratogenic effects have been noted with 2- and 4-aminophenol in the hamster, but 3-aminophenol was without effect in the hamster and rat (129,130). 4-Aminophenol is known to inhibit DNA synthesis and alter DNA structure in human lymphoblasts (131,132) and is mutagenic in mouse micronuclei tests (133). The aminophenols have been shown to be genotoxic, as evidenced by the induction of sister chromatid exchanges (134,135), but they also exert a protective effect against DNA interaction with other noxious chemicals (136). After assessment of available data a recent report stated that the aminophenols were safe as cosmetic ingredients in their present uses and concentrations (137).

Obviously, care should be taken in handling these compounds with the wearing of chemical-resistant gloves and safety goggles; prolonged exposure should be avoided. Contaminated clothing should be removed immediately and the affected area washed thoroughly with running water for at least 10 minutes.

Because the aminophenols are oxidized easily, they tend to remove oxygen from solutions. Hence, if they are released from industrial waste waters into streams and rivers, they will deplete the capacity of these environments to sustain aquatic life. Concern has also been raised that chlorination of drinking water may enhance the toxicity of aminophenols present as pollutants (138); chlorinated aminophenols are known to be more toxic (139).

The addition of slaked lime (140) and the initiation of polymerization reactions with H₂O₂ and ferric or stannous salts (141) are techniques employed to remove aminophenols from waste waters. An enzymatic method using horseradish peroxidase to crosslink and precipitate the compounds as insoluble polymers has also been studied (142). Biological degradation of 3-aminophenol has been carried out in aeration tanks using adapted microflora (over a 4 month period) from activated sludge (143); and other microbial degradation techniques are under investigation (144–146).

Uses

The aminophenols are versatile intermediates and their principal use is as synthesis precursors; their products are represented among virtually every class of stain and dye.

Both 2- and 4-aminophenols are strong reducing agents and are employed as photographic developers under the trade names of Atomal and Ortol (2-aminophenol); Activol, Azol, Certinal, Citol, Paranol, Rodinol, Unal, and Ursol P (4-aminophenol); they may be used alone or in combination with hydroquinone. The oxalate salt of 4-aminophenol is marketed under the name of Kodelon. They also act as corrosion inhibitors in paints (147) and as anticorrosion-lubricating agents in two-cycle engine fuels (148).

As a result of the close proximity of the amino and hydroxyl groups on the benzene ring and their ease of condensation with suitable reagents, 2-aminophenol is a principal intermediate in the synthesis of such heterocyclic systems as oxyquinolines, phenoxazines, and benzoxazoles. The last-named compounds have been used as inflammation inhibitors (149), and other derivatives have potential as antiallergic agents (150). In addition, 2-aminophenol is specifically used for shading leather, fur, and hair from grays to yellowish brown. It has also found application in the determination and extraction of certain precious metals (151,152).

3-Aminophenol has been used as a stabilizer of chlorine-containing thermoplastics (153), although its principal use is as an intermediate in the production of 4-amino-2-hydroxybenzoic acid [65-49-6], a tuberculostat. This isomer is also employed as a hair colorant and as a coupler molecule in hair dyes (154,155).

Nitrogen-substituted 4-aminophenols have long been known as antipyretics and analgesics, and the production of these derivatives represents significant use of this compound. 4-Aminophenol is also used as a wood stain , imparting a roselike color to timber (156), and as a dyeing agent for fur and feathers.

Derivatives

The derivatives of the aminophenols have important uses both in the photographic and the pharmaceutical industries. They are also extensively employed as precursors and intermediates in the synthesis of more complicated molecules, especially those used in the staining and dye industry. All of the major classes of dyes have representatives that incorporate substituted aminophenols; these compounds produced commercially as dye intermediates have been reviewed (157). Details of the more commonly encountered derivatives of the aminophenols can be found in standard organic chemistry texts (25,158). A few examples, which have specific uses or are manufactured in large quantities, are discussed in detail in the following (see Table 6).

Table 6. Derivatives of Aminophenols

Common name	Structure number	CAS Registry Number	Molecular formula	Molecular weight	Melting point, °C	Boiling point ^a , °C
Derivatives of 2-aminophenol						
2-amino-4-nitrophenol	(9)	[99-57-0]	C ₆ H ₅ N ₂ O ₃	154.13	80–90	
2-amino-4,6-dinitrophenol	(10)	[96-91-3]	C ₆ H ₅ N ₃ O ₅	199.13	169–170	
2-amino-4,6-dichlorophenol	(11)	[527-62-8]	C ₆ H ₅ Cl ₂ NO	168.15	95–96	
2,4-diaminophenol	(12)	[95-86-3]	C ₆ H ₈ N ₂ O	124.14	78–80 ^b	
acetarsone	(13)	[97-44-9]	C ₈ H ₁₀ AsNO ₅	275.08	240–250 ^b	
Derivatives of 3-aminophenol						
3-(N,N-dimethylamino)phenol	(14)	[99-07-0]	C ₈ H ₁₁ NO	137.18	87	265–268 206 (13.3) 194 (6.7) 153 (0.7) 170 (1.6)
3-(N-methylamino)phenol	(15)	[14703-69-6]	C ₇ H ₉ NO	123.15		
3-(N,N-diethylamino)phenol	(16)	[91-68-9]	C ₁₀ H ₁₅ NO	165.23	78	276–280 209–211 (1.6) 340
3-(N-phenylamino)phenol	(17)	[101-18-8]	C ₁₂ H ₁₁ NO	185.22	81.5–82	
4-amino-2-hydroxybenzoic acid	(18)	[65-49-6]	C ₇ H ₇ NO ₃	153.13	150–151	
Derivatives of 4-aminophenol						
4-(N-methylamino)phenol	(19)	[150-75-4]	C ₇ H ₉ NO	123.15	87	168–169 (2)
4-(N,N-dimethylamino)phenol	(20)	[619-60-3]	C ₈ H ₁₁ NO	137.18	75–76	101–103 (0.067)
4-hydroxyacetanilide	(21)	[103-90-2]	C ₈ H ₉ NO ₂	151.15	169–171	
4-ethoxyacetanilide	(22)	[62-44-2]	C ₁₀ H ₁₃ NO ₂	179.21	134–135	
N-(4-hydroxyphenyl)glycine	(23)	[122-87-2]	C ₈ H ₉ NO ₃	167.16	245–247 ^b	

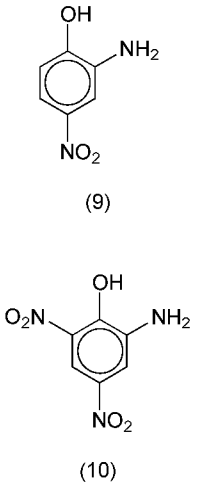
^a At 101.3 kPa (760 mm Hg) unless otherwise noted in parentheses. Values in parentheses are in the kPa. To convert kPa to mm Hg, multiply by 7.5.
^b Decomposes.

DERIVATIVES OF 2-AMINOPHENOL

2-Amino-4-nitrophenol. This derivative, 2-hydroxy-5-nitroaniline (9), forms orange prisms from water. These prisms are hydrated with one water of crystallization, mp 80–90°C, and can be dehydrated over sulfuric acid to the anhydrous form, mp 143–145°C. The compound is soluble in ethanol, diethyl ether, acetic acid, and warm benzene and slightly soluble in water.

2-Amino-4-nitrophenol is produced commercially by the partial reduction of 2,4-dinitrophenol. This reduction may be achieved electrolytically using vanadium (159) or chemically with polysulfide, sodium hydrosulfide, or hydrazine and copper (160). Alternatively, 2-acetamidophenol or 2-methylbenzoxazole may be nitrated in sulfuric acid to yield a mixture of 4- and 5-nitro derivatives that are then separated and hydrolyzed with sodium hydroxide (161).

The major use of this compound is in the production of mordant and acid dyes. 2-Amino-4-nitrophenol also has found limited use as an antioxidant and light stabilizer in butyl rubbers and as a catalyst in the manufacture of hexadiene. The compound has been shown to be a skin irritant and continuous exposure should be avoided. Toxicological studies indicate that it is nonaccumulative (162).



2-Amino-4,6-dinitrophenol. This derivative (10), also known as picramic acid, forms dark red needles from ethanol and prisms from

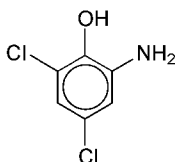
chloroform. The compound flashes at 210°C in contact with an open flame, ignites rapidly and burns relatively fast. 2-Amino-4,6-dinitrophenol is soluble in glacial acetic acid, water, ethanol, benzene, and aniline and is sparingly soluble in diethyl ether and chloroform.

The compound can be prepared from 2,4,6-trinitrophenol (picric acid [88-89-1]) by reduction with sodium hydrosulfide (163), with ammonia–hydrogen sulfide followed by acetic acid neutralization of the ammonium salt (164), with ethanolic hydrazine and copper (165), or electrolytically with vanadium sulfate in alcoholic sulfuric acid (159). Heating 4,6-dinitro-2-benzamidophenol in concentrated HCl at 140°C also yields picramic acid (166).

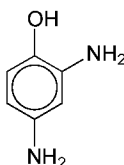
2-Amino-4,6-dinitrophenol is an important intermediate in the manufacture of colorants, especially mordant dyes. It has also been used as an indicator dye in titrations (yellow with acid, red with alkali) and as a reagent for albumin determination.

2-Amino-4,6-dichlorophenol. This compound (11) forms long white needles from carbon disulfide, and aggregate spheres from benzene. It sublimes at 70–80°C (8 Pa = 0.06 mm Hg) and decomposes above 109°C. It is freely soluble in benzene and carbon disulfide, and is sparingly soluble in petroleum ether, water, and ethanol. The free base is unstable and the hydrochloride salt (mp 280–285°C, dec) is employed commercially.

Industrial production is by reduction of the corresponding nitrophenol with iron or hydrazine (167,168). 2-Amino-4,6-dichlorophenol finds important use as an azo-dye intermediate (see AZO DYES).



(11)

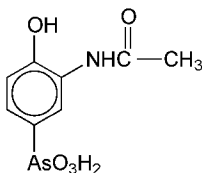


(12)

2,4-Diaminophenol. 4-Hydroxy-*m*-phenylenediamine [95-86-3] (12) forms leaflets that darken on exposure to air. It is soluble in acid, alkali, ethanol, and acetone and is sparingly soluble in chloroform, diethyl ether, and ligroin. 2,4-Diaminophenol usually is sold as the sulfate [74283-34-4] (Diamol) or dihydrochloride salt [137-09-7] (Acrol, Amidol). 2,4-Diaminophenol can be prepared from 2,4-dinitrophenol by catalytic hydrogenation or, less conveniently, by metal reduction in acid solution (Büchamp method) (169,170). Alternatively, electrolytic reduction and subsequent hydroxylation of 1,3-dinitrobenzene or 3-nitroaniline in sulfuric acid can be undertaken (171,172).

The dihydrochloride salt is used as a photographic developer. It also is employed as an intermediate in the manufacture of fur dyes, in hair dyeing, as a reagent in testing for ammonia and formaldehyde, and as an oxygen scavenger in water to prevent boiler corrosion (173).

Acetarstone. Acetarstone (3-acetamido-4-hydroxyphenyl arsonic acid) (13), also known as acetarsol, stovarsol, and Ehrlich 594, forms white prisms from water.



(13)

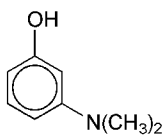
The compound is odorless with a faintly acidic taste; it is practically insoluble in water, ethanol and dilute acids but freely soluble in dilute aqueous alkali with dissociation constants, pK_a , 3.73, 7.9, 9.3. The compound is prepared by sodium hydrosulfite reduction of 3-nitro-4-hydroxyphenylarsonic acid [121-19-7] and then acetylation in aqueous suspension with acetic anhydride at 50–55°C for 2 h (174,175).

Salts of acetarstone are used in the treatment of intestinal amoebiasis, vaginal trichomoniasis, and necrotizing ulcerative gingivitis (Vincent's angina). The diethylamine salt (acetylarsan [534-33-8]) has antisyphilitic properties. Because of toxicity problems, safer drugs have been developed. Oral LD₅₀ in rabbits is 150 mg/kg.

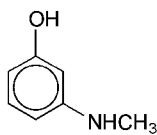
DERIVATIVES OF 3-AMINOPHENOL

3-(*N,N*-Dimethylamino)phenol. 3-Hydroxy-*N,N*-dimethylaniline (14) forms white needles and is soluble in alkali, mineral acid, ethanol, diethyl ether, acetone, and benzene and practically insoluble in water.

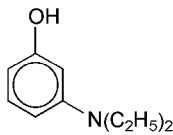
It can be prepared by heating resorcinol with an aqueous solution of dimethylamine and its hydrochloride at 200°C under pressure for 12 h (176). The treatment of dimethylaniline with oleum at 55–60°C, followed by fusion with sodium hydroxide at 270–300°C, also gives 3-(*N,N*-dimethylamino)phenol (177). In addition, 3-aminophenol may be methylated with dimethyl sulfate under neutral conditions, or its hydrochloride salt heated with methanol at 170°C under pressure for 8 h to give the desired product (178). The compound is used primarily as an intermediate in the production of basic (Red 3 and Red 11) and mordant (Red 77) dyes.



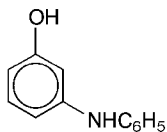
(14)



(15)



(16)



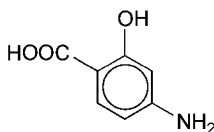
(17)

3-(*N*-Methylamino)phenol. This derivative (15) is easily soluble in ethyl acetate, ethanol, diethyl ether, and benzene. It is also soluble in hot water, but only sparingly soluble in cold water. Industrial synthesis is by heating 3-(*N*-methylamino)benzenesulfonic acid with sodium hydroxide at 200–220°C (179) or by the reaction of resorcinol with methylamine in the presence of aqueous phosphoric acid at 200°C (180).

3-(*N,N*-Diethylamino)phenol. This derivative (16) forms rhombic bipyramidal crystals. Industrial synthesis is analogous to the previously described synthesis of 3-(*N,N*-dimethylamino)phenol from resorcinol and diethylamine, by reaction of 3-(*N,N*-diethylamino)benzenesulfonic acid with sodium hydroxide, or by alkylation of 3-aminophenol hydrochloride with ethanol.

3-(*N*-Phenylamino)phenol. This phenol (17) is slightly soluble in ethanol, diethyl ether, acetone, benzene, and water. The compound is made by heating resorcinol and aniline at 200°C in the presence of aqueous phosphoric acid or calcium chloride. In another process, 3-aminophenol is heated with aniline hydrochloride at 210–215°C (181).

4-Amino-2-hydroxybenzoic acid. This derivative (18) more commonly known as 4-aminosalicylic acid, forms white crystals from ethanol, melts with effervescence and darkens on exposure to light and air. A reddish-brown crystalline powder is obtained on recrystallization from ethanol–diethyl ether. The compound is soluble in dilute solutions of nitric acid and sodium hydroxide, ethanol, and acetone; slightly soluble in water and diethyl ether; and virtually insoluble in benzene, chloroform or carbon tetrachloride. It is unstable in aqueous solution and decarboxylates to form 3-aminophenol. Because of the instability of the free acid, it is usually prepared as the hydrochloride salt, mp 224 °C (dec), dissociation constant pK_a 3.25.



(18)

4-Amino-2-hydroxybenzoic acid is manufactured by carboxylation of 3-aminophenol under pressure with ammonium carbonate at 110 °C (182) or with potassium bicarbonate and carbon dioxide at 85–90°C (183) with subsequent acidification.

The major use of this compound is as a bacteriostatic agent against tubercle bacilli. The compound also is used as an adjunct to streptomycin and isoniazid. The free acid and its sodium, potassium, and calcium salts are marketed under many trade names (eg, Aminox, Apacil, Deapasil, Paramycin, Parasalil, Pasnodia, Rezipas, Sanipiol-4, Tubersan). Up to 10–15 g of the sodium salt may be administered each day, although prolonged use may give rise to toxic symptoms. Oral LD₅₀ of the free acid in mice is 4 g/kg.

DERIVATIVES OF 4-AMINOPHENOL

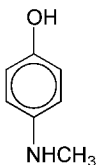
4-(*N*-Methylamino)phenol. This derivative, also named 4-hydroxy-*N*-methylaniline (19), forms needles from benzene which are slightly soluble in ethanol and insoluble in diethyl ether. Industrial synthesis involves decarboxylation of *N*-(4-hydroxyphenyl)glycine [122-87-2] at elevated temperature in such solvents as chlorobenzene–cyclohexanone (184,185). It also can be prepared by the methylation of 4-aminophenol, or from methylamine [74-89-5] by heating with 4-chlorophenol [106-48-9] and copper sulfate at 135°C in aqueous solution, or with hydroquinone [123-31-9] at 200–250°C in alcoholic solution (186).

Its chief use is as a component in photographic developers. Because the free compound is unstable in air and light, it is usually marketed as the sulfate salt [55-55-0], Metol, mp 260°C (dec.). It also finds application as an intermediate for fur and hair dyes and, under certain circumstances, as a corrosion inhibitor for steel. Prolonged exposure to 4-(*N*-methylamino)phenol has been associated with the development of dermatitis and allergies.

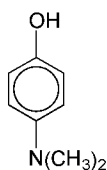
4-(*N,N*-Dimethylamino)phenol. 4-Hydroxy-*N,N*-dimethylaniline (20) forms large rhombic crystals from diethyl ether–hexane or diethyl ether–ligroin. It forms a salt with sulfuric acid, mp 208–210°C (187).

Methylation of 4-aminophenol with a methyl halide under pressure produces 4-(*N,N*-dimethylamino)phenol. The competing product, 4-hydroxyphenyltrimethyl ammonium halide (or the corresponding base), also yields 4-(*N,N*-dimethylamino)phenol on distillation. Alternatively, it can be synthesized by dealkylation of 4-methoxy-*N,N*-dimethylaniline [701-56-4] with hydroiodic acid at reflux temperature for 10 h (188) or by the photodecomposition of 4-dimethylaminobenzene diazonium tetrafluoroborate [24564-52-1] (187).

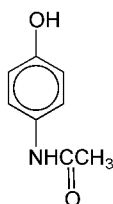
The compound is an intermediate in several synthetic reactions and recently has found extensive use in experimental toxicity studies in animals. It has been shown to cause methemoglobinemia; its metabolism in humans has been discussed (189,190).



(19)



(20)



(21)

4-Hydroxyacetanilide. This derivative (21), also known as 4-acetamidophenol, acetaminophen, or paracetamol, forms large white monoclinic prisms from water. The compound is odorless and has a bitter taste. 4-Hydroxyacetanilide is insoluble in petroleum ether, pentane, and benzene; slightly soluble in diethyl ether and cold water, and soluble in hot water, alcohols, dimethylformamide, 1,2-dichloroethane, acetone, and ethyl acetate. The dissociation constant, pK_a , is 9.5 (25°C).

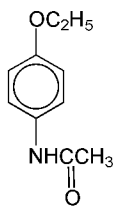
Production is by the acetylation of 4-aminophenol. This can be achieved with acetic acid and acetic anhydride at 80°C (191), with acetic acid anhydride in pyridine at 100°C (192), with acetyl chloride and pyridine in toluene at 60°C (193), or by the action of ketene in alcoholic suspension. 4-Hydroxyacetanilide also may be synthesized directly from 4-nitrophenol. The available reduction–acetylation systems include tin with acetic acid, hydrogenation over Pd–C in acetic anhydride, and hydrogenation over platinum in acetic acid (194,195). Other routes include rearrangement of 4-hydroxyacetophenone hydrazone with sodium nitrite in sulfuric acid and the electrolytic hydroxylation of acetanilide [103-84-4] (196).

4-Hydroxyacetanilide is used as an intermediate in the manufacture of azo dyes (qv) and photographic chemicals. The compound possesses antipyretic and analgesic properties and is used widely in this context. Typical formulations containing 4-hydroxyacetanilide include Acetalgin, Cetadol, Dirox, Febrilix, Hedex, Panadol, Tylenol, and Valadol. The oral LD_{50} in rats is 3.7 g/kg.

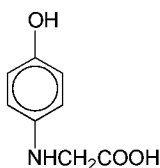
4-Ethoxyacetanilide. This compound (22), also known as phenacetin, is a white crystalline powder. The compound is odorless and has a slightly bitter taste. It is sparingly soluble in cold water and more soluble in hot water, ethanol, diethyl ether, and chloroform. At relative humidities between 15 and 90% the equilibrium moisture content is about 2% (25°C).

The main production route to 4-ethoxyacetanilide is by catalytic reduction of 4-nitrophenetole [100-29-8] with hydrogen and subsequent acetylation using acetic anhydride. The compound also can be synthesized by ethylating 4-nitrophenol with ethyl sulfate in alkali, reducing the nitro group to an amino group with iron in acid and then acetylating by boiling with glacial acetic acid (197). Alternatively, 4-aminophenol may be ethylated with ethyl iodide in alcoholic alkali and the resulting 4-phenetidine [156-43-4] then acetylated. The acetylation also may be carried out first, followed by the ethylation.

4-Ethoxyacetanilide possesses both antipyretic and analgesic properties, but it is of little value for the relief of severe pain. Its use for prolonged periods should be avoided because one of its minor metabolites (2-hydroxyphenetidine) is nephrotoxic and may be involved in the formation of methemoglobinemia. The oral LD_{50} in rats is 1.65 g/kg (198).



(22)



(23)

N-(4-Hydroxyphenyl)glycine. This derivative (23) forms aggregate spheres or shiny leaflets from water. It turns brown at 200°C, begins to melt at 220°C, and melts completely with decomposition at 245–247°C. The compound is soluble in alkali and mineral acid and sparingly soluble in water, glacial acetic acid, ethyl acetate, ethanol, diethyl ether, acetone, chloroform, and benzene.

N-(4-Hydroxyphenyl)glycine can be prepared from 4-aminophenol and chloroacetic acid (199,200) or by alkaline hydrolysis of the corresponding nitrile with subsequent elimination of ammonia (201).

N-(4-Hydroxyphenyl)glycine is used as a photographic developer under the trade names of Glycine, Iconyl, and Monazol. It is also applied as a photoresist in the dye industry and serves as an intermediate in the production of 4-(N-methylamino)phenol (Metol) by liberation of CO_2 .

N-(4-Hydroxyphenyl)glycine is used in analytical chemistry for the determination of iron, phosphorus, and silicon, and as an acid indicator in bacteriology. Prolonged exposure to this compound may result in kidney damage (202).

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AMINO RESINS AND PLASTICS

Amino resins are thermosetting polymers made by combining an aldehyde with a compound containing an amino (—NH_2) group. Urea–formaldehyde (U F) accounts for over 80% of amino resins; melamine–formaldehyde accounts for most of the rest. Other aldehydes and other amino compounds are used to a very minor extent. The first commercially important amino resin appeared about 1930, or some 20 years after the introduction of phenol–formaldehyde resins and plastics (see PHENOLIC RESINS).

The principal attractions of amino resins and plastics are water solubility before curing, which allows easy application to and with many other materials, colorlessness, which allows unlimited colorability with dyes and pigments, excellent solvent resistance in the cured state, outstanding hardness and abrasion resistance, and good heat resistance. Limitations of these materials include release of formaldehyde during cure and, in some cases, such as in foamed insulation, after cure, and poor outdoor weatherability for urea moldings. Repeated cycling of wet and dry conditions causes surface cracks. Melamine moldings have relatively good outdoor weatherability.

Amino resins are manufactured throughout the industrialized world to provide a wide variety of useful products. Adhesives (qv), representing the largest single market, are used to make plywood, chipboard, and sawdust board. Other types are used to make laminated wood beams, parquet flooring, and for furniture assembly (see WOOD BASED COMPOSITES AND LAMINATES).

Some amino resins are used as additives to modify the properties of other materials. For example, a small amount of amino resin added to textile fabric imparts the familiar wash-and-wear qualities to shirts and dresses. Automobile tires are strengthened by amino resins which improve the adhesion of rubber to tire cord (qv). A racing sailboat may have a better chance to win because the sails of Dacron polyester have been treated with an amino resin (1). Amino resins can improve the strength of paper even when it is wet. Molding compounds based on amino resins are used for parts of electrical devices, bottle and jar caps, molded plastic dinnerware, and buttons.

Amino resins are also often used for the cure of other resins such as alkyds and reactive acrylic polymers. These polymer systems may contain 5–50% of the amino resin and are commonly used in the flexible backings found on carpets and draperies, as well as in protective surface coatings, particularly the durable baked enamels of appliances, automobiles, etc.

The term amino resin is usually applied to the broad class of materials regardless of application, whereas the term aminoplast or sometimes amino plastic is more commonly applied to thermosetting molding compounds based on amino resins. Amino plastics and resins have been in use since the 1920s. Compared to other segments of the plastics industry, they are mature products, and their growth rate is only about half of that of the plastics industry as a whole. They account for about 3% of the United States plastics and resins production.

History. The basic chemistry of amino resins was established as early as 1908 (2), but the first commercial product, a molding compound, was patented in England (3) only in 1925. It was based on a resin made from an equimolar mixture of urea and thiourea and reinforced with purified cellulose fiber and was trademarked Beetle (indicating it could "beat all" others). Patent rights were acquired by the American Cyanamid Company along with the Beetle trademark, and by 1930 a similar molding compound was being marketed in the United States. The new product was hard and not easily stained and was available in light, translucent colors; furthermore, it had no objectionable phenolic odor. The use of thiourea improved gloss and water resistance, but stained the steel molds. As amino resin technology progressed the amount of thiourea in the formulation could be reduced and finally eliminated altogether.

In the early 1920s, experimentation with urea–formaldehyde resins [9011-05-6] in Germany (4) and Austria (5,6) led to the discovery that these resins might be cast into beautiful clear transparent sheets, and it was proposed that this new synthetic material might serve as an organic glass (5,6). In fact, an experimental product called Pollopas was introduced, but lack of sufficient water resistance prevented commercialization. Melamine–formaldehyde resin [9003-08-1] does have better water resistance but the market for synthetic glass was taken over by new thermoplastic materials such as polystyrene and poly(methyl methacrylate) (see METHACRYLIC POLYMERS; STYRENE PLASTICS).

Melamine resins were introduced about ten years after the Beetle molding compound. They were very similar to those based on urea but had superior qualities. Henkel in Germany was issued a patent for a melamine resin in 1936 (7). Melamine resins rapidly supplanted urea resins and were soon used in molding, laminating, and bonding formulations, as well as for textile and paper treatments. The remarkable stability of the symmetrical triazine ring made these products resistant to chemical change once the resin had been cured to the insoluble, cross-linked state.

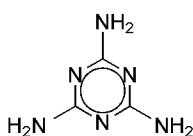
Prior to the rapid expansion of thermoplastics following World War II, amino plastics served a broad range of applications in molding, laminating, and bonding. As the newer and more versatile thermoplastic materials moved into these markets, aminos became more and more restricted to applications demanding some specific property best offered by the thermosetting amino resins. Current sales patterns are very specific. Urea molding powders find application in moldings for electrical devices and in closures for jars and bottles. Melamine molding compound is used principally for molded plastic dinnerware. Urea resins have retained their use in electrical wiring devices because of good electrical properties, good heat resistance, and an availability of colors not obtainable with phenolics. Urea–formaldehyde resins are useful as closures because of their excellent resistance to oils, fats, and waxes often found in cosmetics, and their availability in a broad range of colors. Melamine plastic is used for molded dinnerware primarily because of outstanding hardness, water resistance, and stain resistance. Melamine –formaldehyde is the hardest commercial plastic material.

Aminoplasts and other thermosetting plastics are molded by an automatic injection molding process similar to that used for thermoplastics, but with an important difference (8). Instead of being plasticized in a hot cylinder and then injected into a much cooler mold cavity, the thermosets are plasticized in a warm cylinder and then injected into a hot mold cavity where the chemical reaction of cure sets the resin to the solid state. The process is best applied to relatively small moldings. Melamine plastic dinnerware is still molded by standard compression-molding techniques. The great advantage of injection molding is that it reduces costs by eliminating manual labor, thereby placing the amino resins in a better position to compete with thermoplastics (see PLASTICS PROCESSING).

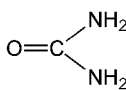
The future for amino resins and plastics seems secure because they can provide qualities that are not easily obtained in other ways. New developments will probably be in the areas of more highly specialized materials for treating textiles, paper, etc, and for use with other resins in the formulation of surface coatings, where a small amount of an amino resin can significantly increase the value of a more basic material. Additionally, since amino resins contain a large proportion of nitrogen, a widely abundant element, they may be in a better position to compete with other plastics as raw materials based on carbon compounds become more costly.

Raw Materials

Most amino resins are based on the reaction of formaldehyde [50-00-0] with urea [57-13-6] or melamine [108-78-1]

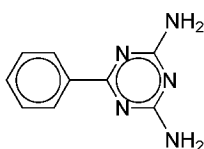


melamine

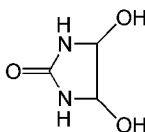


urea

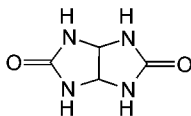
Although formaldehyde will combine with many other amines, amides, and aminotriazines to form useful products, only a few are used and are of minor importance compared to products based on urea and melamine. Benzoguanamine [91-76-9], for example, is used in amino resins for coatings because it provides excellent resistance to laundry detergent, a definite advantage in coatings for automatic washing machines. Dihydroxyethylene urea [3720-97-6] is used for making amino resins that provide wash-and-wear properties in clothing. Glycoluril [496-46-8] resins provide coatings with high film flexibility.



benzoguanamine



dihydroxyethyleneurea



glycoluril

Aniline–formaldehyde resins were once quite important because of their excellent electrical properties, but their markets have been taken over by newer thermoplastic materials. Nevertheless, some aniline resins are still used as modifiers for other resins. Acrylamide (qv) occupies a unique position in the amino resins field since it not only contains a formaldehyde reactive site, but also a polymerizable double bond. Thus it forms a bridge between the formaldehyde condensation polymers and the versatile vinyl polymers and copolymers.

In the sense that formaldehyde can supply a methylene link between two molecules, it is difunctional. Each amino group has two replaceable hydrogens that can react with formaldehyde; hence, it also is difunctional. Since the amino compounds commonly used for making amino resins, urea, and melamine contain two and three amino groups, they are polyfunctional and react with formaldehyde to form three-dimensional, cross-linked polymer structures. Compounds with a single amino group such as aniline or toluenesulfonamide can usually react with formaldehyde to form only linear polymer chains. However, in the presence of an acid catalyst at higher temperatures, the aromatic ring of aniline may react with formaldehyde to produce a cross-linked polymer.

Urea. Urea (carbamide) $\text{CH}_4\text{N}_2\text{O}$, is the most important building block for amino resins because urea–formaldehyde is the largest selling amino resin, and urea is the raw material for melamine, the amino compound used in the next largest selling type of amino resin. Urea is also used to make a variety of other amino compounds, such as ethyleneurea, and other cyclic derivatives used for amino resins for treating textiles. They are discussed later.

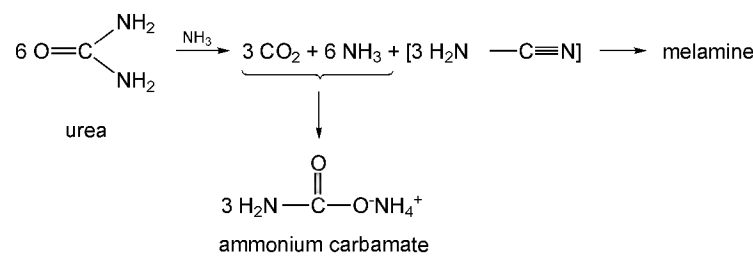
Urea is soluble in water, and the crystalline solid is somewhat hygroscopic, tending to cake when exposed to a humid atmosphere. For this reason, urea is frequently pelletized or prilled (formed into little beads) to avoid caking and making it easy to handle.

Only about 10% of the total urea production is used for amino resins, which thus appear to have a secure source of low cost raw material. Urea is made by the reaction of carbon dioxide and ammonia at high temperature and pressure to yield a mixture of urea and ammonium carbamate; the latter is recycled.



Melamine. Melamine (cyanurotriamide, 2,4,6-triamino-*s*-triazine) $\text{C}_3\text{H}_3\text{N}_3$, is a white crystalline solid, melting at approximately 350°C with vaporization, only slightly soluble in water. The commercial product, recrystallized grade, is at least 99% pure. Melamine was synthesized early in the development of organic chemistry, but it remained of theoretical interest until it was found to be a useful constituent of amino resins. Melamine was first made commercially from dicyandiamide [461-58-5] (see CYANAMIDES), but is now made from urea, a much cheaper starting material (9–12) (see also CYANURIC AND ISOCYANURIC ACIDS).

Urea is dehydrated to cyanamide which trimerizes to melamine in an atmosphere of ammonia to suppress the formation of deamination products. The ammonium carbamate [1111-78-0] also formed is recycled and converted to urea. For this reason the manufacture of melamine is usually integrated with much larger facilities making ammonia and urea.



Since melamine resins are derived from urea, they are more costly and are therefore restricted to applications requiring superior performance. Essentially all of the melamine produced is used for making amino resins and plastics.

Formaldehyde. Pure formaldehyde, CH₂O, is a colorless, pungent smelling reactive gas (see FORMALDEHYDE). The commercial product is handled either as solid polymer, paraformaldehyde (13), or in aqueous or alcoholic solutions. Marketed under the trade name Formcel, solutions in methanol, *n*-butanol, and isobutyl alcohol, made by Hoechst-Celanese, are widely used for making alcohol-modified urea and melamine resins for surface coatings and treating textiles.

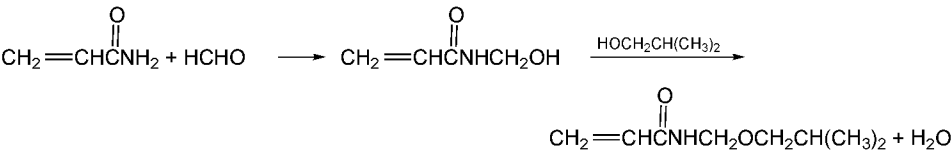
Aqueous formaldehyde, known as formalin, is usually 37 wt % formaldehyde, though more concentrated solutions are available. Formalin is the general-purpose formaldehyde of commerce supplied unstabilized or methanol-stabilized. The latter may be stored at room temperature without precipitation of solid formaldehyde polymers because it contains 5–10% methyl alcohol. The uninhibited type must be maintained at a temperature of at least 32°C to prevent the separation of solid formaldehyde polymers. Large quantities are often supplied in more concentrated solutions. Formalin at 44, 50, or even 56% may be used to reduce shipping costs and improve manufacturing efficiency. Heated storage tanks must be used. For example, formalin containing 50% formaldehyde must be kept at a temperature of 55°C to avoid precipitation. Formaldehyde solutions stabilized with urea are used (14), and various other stabilizers have been proposed (15–16). With urea-stabilized formaldehyde the user need only adjust the U : F ratio by adding more urea to produce a urea resin solution ready for use.

Paraformaldehyde [30525-89-4] is a mixture of polyoxymethylene glycols, HO(CH₂O)_{*n*}H, with *n* from 8 to as much as 100. It is commercially available as a powder (95%) and as flake (91%). The remainder is a mixture of water and methanol. Paraformaldehyde is an unstable polymer that easily regenerates formaldehyde in solution. Under alkaline conditions, the chains depolymerize from the ends, whereas in acid solution the chains are randomly cleaved (17). Paraformaldehyde is often used when the presence of a large amount of water should be avoided as in the preparation of alkylated amino resins for coatings. Formaldehyde may also exist in the form of the cyclic trimer trioxane [110-88-3]. This is a fairly stable compound that does not easily release formaldehyde, hence it is not used as a source of formaldehyde for making amino resins.

Approximately 25% of the formaldehyde produced in the United States is used in the manufacture of amino resins and plastics.

Other Materials. Benzoguanamine and acetoguanamine may be used in place of melamine to achieve greater solubility in organic solvents and greater chemical resistance. Aniline and toluenesulfonamide react with formaldehyde to form thermoplastic resins. They are not used alone, but rather as plasticizers (qv) for other resins including melamine and urea–formaldehyde. The plasticizer may be made separately or formed *in situ* during preparation of the primary resin.

Acrylamide [79-06-1] is an interesting monomer for use with amino resins; the vinyl group is active in free-radical catalyzed addition polymerizations, whereas the —NH₂ group is active in condensations with formaldehyde. Many patents describe methods of making cross-linked polymers with acrylamide by taking advantage of both vinyl polymerization and condensation with formaldehyde. For example, acrylamide reacts readily with formaldehyde to form *N*-methylolacrylamide [924-42-5] which gives the corresponding isobutyl ether with isobutyl alcohol.



This compound is soluble in most organic solvents and may be easily copolymerized with other vinyl monomers to introduce reactive side groups on the polymer chain (18). Such reactive polymer chains may then be used to modify other polymers including other amino resins. It may be desirable to produce the cross-links first. Thus, *N*-methylolacrylamide can react with more acrylamide to produce methylenebisacrylamide, a tetrafunctional vinyl monomer.

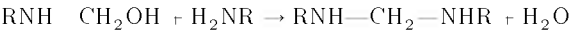


Chemistry of Resin Formation

The first step in the formation of resins and plastics from formaldehyde and amino compounds is the addition of formaldehyde to introduce the hydroxymethyl group, known as methylation or hydroxymethylation:



The second step is a condensation reaction that involves the linking together of monomer units with the liberation of water to form a dimer, a polymer chain, or a vast network. This is usually referred to as methylene bridge formation, polymerization, resinification, or simply cure, and is illustrated in the following equation:



Success in making and using amino resins largely depends on the precise control of these two chemical reactions. Consequently, these reactions have been much studied (19–30).

The first reaction, the addition of formaldehyde to the amino compound, is catalyzed by either acids or bases. Hence, it takes place over the entire pH range. The second reaction joins the amino units with methylene links and is catalyzed only by acids. The rates of these reactions have been studied over a broad range of pH (28). The results are presented in Figure 1.

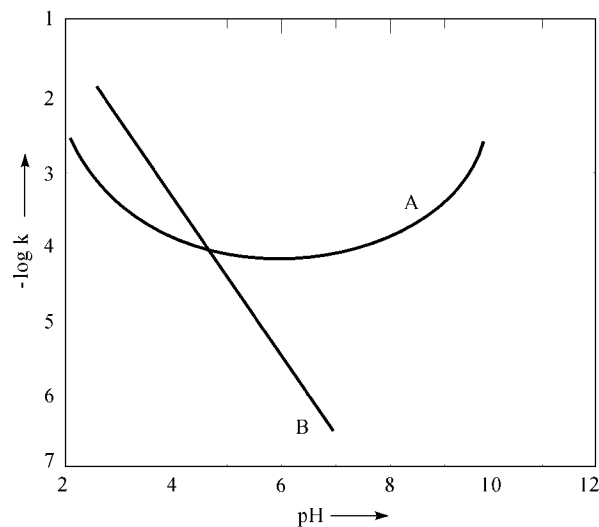


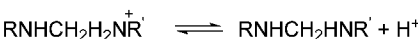
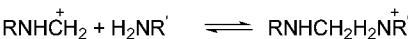
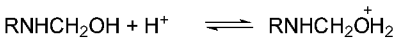
Fig. 1. Influence of pH on A, the addition reaction of urea and formaldehyde (1:1); and B, the condensation of methylolurea with the amino hydrogen of a neighboring urea molecule. Temperature = 35°C; 0.1 M aq.

The same study also examined some of the subsequent reactions involved in the formation of more complex U F condensation products. Rate constants for these reactions at 35°C are shown in Table 1.

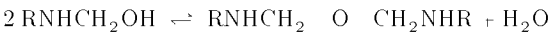
Table 1. Urea–Formaldehyde (U/F) Reaction Rate Constants

Reaction at 35°C and pH 4.0	k, L (mol·s)
U + F → U/F	4.4 × 10 ⁻⁴
U F + U → U-CH ₂ -U	3.3 × 10 ⁻⁴
U F + U F → U-CH ₂ -U F	0.85 × 10 ⁻⁴
U F ₂ + U F → FU-CH ₂ -U F	0.5 × 10 ⁻⁴
U F ₂ + U F ₂ → FU-CH ₂ -U F ₂	<3 × 10 ⁻⁶

The methylol compounds produced by these reactions are relatively stable under neutral or alkaline conditions, but undergo condensation, forming polymeric products under acid conditions. Consequently, the first step in making an amino plastic is usually carried out under alkaline conditions. The amino compound and formaldehyde are combined and form a stable resin intermediate that may be used as an adhesive or combined with filler to make a molding compound. The second step is the addition of an acidic substance to catalyze the curing reaction, often with the application of heat to cure the amino resin to the solid cross-linked state. In this reaction, the methylol group is probably protonated and a molecule of water lost, giving the intermediate carbonium–imonium ion. This then reacts with an amino group to form a methylene link.



In addition to the two main reactions, ie, methylation and condensation, there are a number of other reactions important for the manufacture and uses of amino resins. For example, two methylol groups may combine to produce a dimethylene ether linkage and liberate a molecule of water:



The dimethylene ether so formed is less stable than the diamino –methylene bridge and may rearrange to form a methylene link and liberate a molecule of formaldehyde.



The simple methylol compounds and the low molecular weight polymers obtained from urea and melamine are soluble in water and quite suitable for the manufacture of adhesives, molding compounds, and some kinds of textile treating resins. However, amino resins for coating applications require compatibility with the film-forming alkyd resins (qv) or copolymer resins with which they must react. Furthermore, even where compatible, the free methylol compounds are often too reactive and unstable for use in a coating-resin formulation that may have to be stored for some time before use. Reaction of the free methylol groups with an alcohol to convert them to alkoxy methyl groups solves both problems.

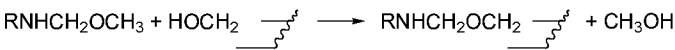
The replacement of the hydrogen of the methylol compound with an alkyl group renders the compound much more soluble in organic solvents and more stable. This reaction is also catalyzed by acids and usually carried out in the presence of considerable excess alcohol to suppress the competing self-condensation reaction. After neutralization of the acid catalyst, the excess alcohol may be stripped or left as a solvent for the amino resin.

The mechanism of the alkylation reaction is similar to curing. The methylol group becomes protonated and dissociates to form a carbonium ion intermediate which may react with alcohol to produce an alkoxy methyl group or with water to revert to the starting material. The amount of water in the reaction mixture should be kept to a minimum since the relative amounts of alcohol and water determine the final equilibrium.

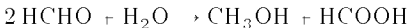
Another way of achieving the desired compatibility with organic solvents is to employ an amino compound having an organic solubilizing group in the molecule, such as benzoguanamine. With one of the –NH₂ groups of melamine replaced with a phenyl group, benzoguanamine-formaldehyde resins [26160-89-4] have some degree of oil solubility even without additives. Nevertheless, benzoguanamine-formaldehyde resins are generally modified with alcohols to provide a still greater range of compatibility with solvent-based surface coatings. Benzoguanamine resins provide a high degree of detergent

resistance together with good ductility and excellent adhesion to metal.

Displacement of a volatile with a nonvolatile alcohol is an important reaction for curing paint films with amino cross-linkers and amino resins on textile fabrics or paper. Following is an example of a methoxymethyl group on an amino resin reacting with a hydroxyl group of a polymer chain.



A troublesome side reaction encountered in the manufacture and use of amino resins is the conversion of formaldehyde to formic acid. Often the reaction mixture of amino compound and formaldehyde must be heated under alkaline conditions. This favors a Cannizzaro reaction in which two molecules of formaldehyde interact to yield one molecule of methanol and one of formic acid.



Unless this reaction is controlled, the solution may become sufficiently acidic to catalyze the condensation reaction causing abnormally high viscosity or premature gelation of the resin solution.

Manufacture

Precise control of the course, speed, and extent of the reaction is essential for successful manufacture. Important factors are: mole ratio of reactants; catalyst (pH of reaction mixture); and reaction time and temperature. Amino resins are usually made by a batch process. The formaldehyde and other reactants are charged to a kettle, the pH adjusted, and the charge heated. Often the pH of the formaldehyde is adjusted before adding the other reactants. Aqueous formaldehyde is most convenient to handle and lowest in cost.

In general, conditions for the first part of the reaction are selected to favor the formation of methylol compounds. After addition of the reactants, the conditions may be adjusted to control the polymerization. The reaction may be stopped to give a stable syrup. This could be an adhesive or laminating resin and might be blended with filler to make a molding compound (see also LAMINATES; REINFORCED PLASTICS). It might also be an intermediate for the manufacture of a more complicated product, such as an alkylated amino resin, for use with other polymers in coatings.

The flow sheet (Fig. 2) illustrates the manufacture of amino resin syrups, cellulose-filled molding compounds, and spray-dried resins.

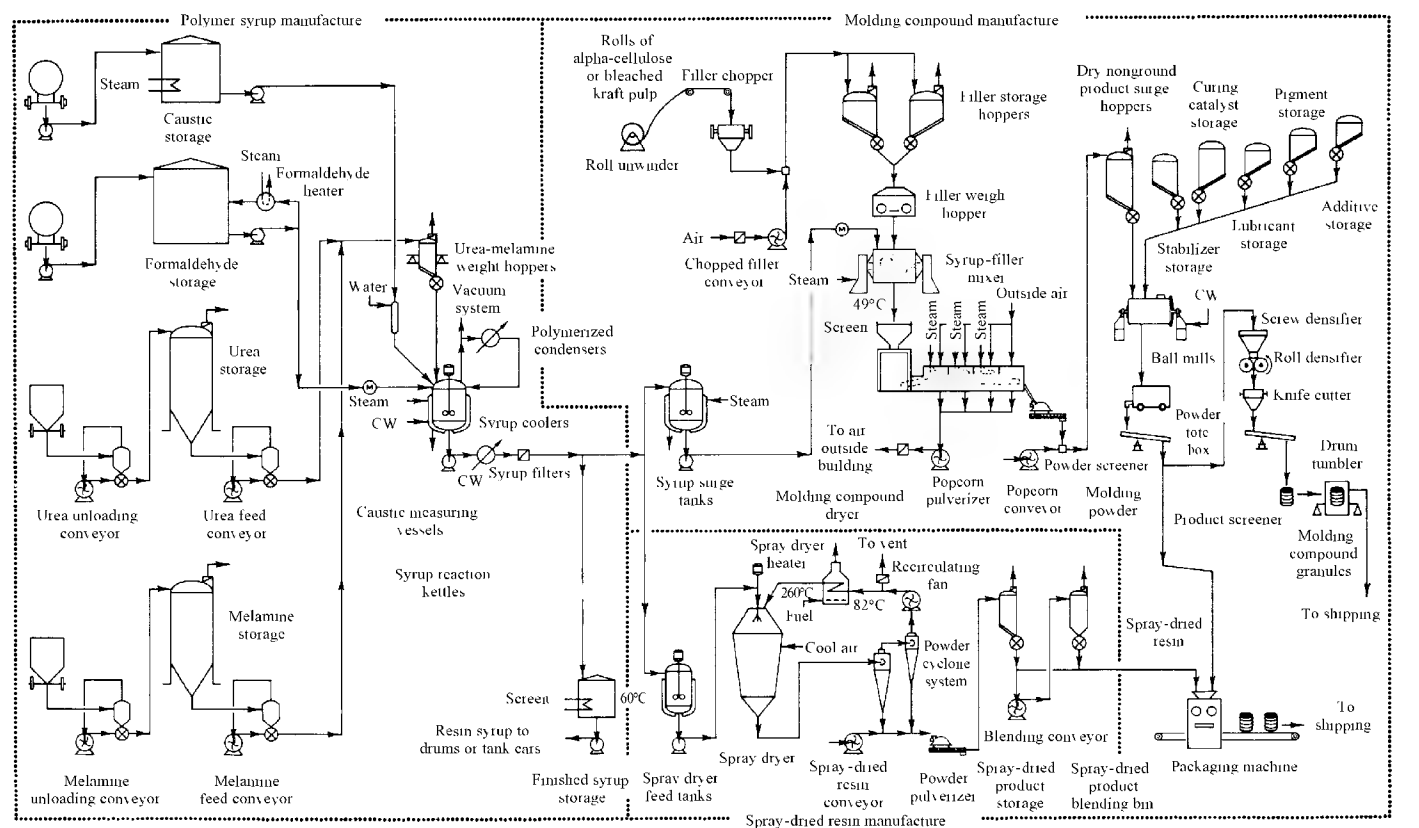


Fig. 2. Urea–formaldehyde and melamine–formaldehyde resin manufacture. C'W = cold water.

Courtesy of Stanford Research Institute.

In the manufacture of amino resins every effort is made to recover and recycle the raw materials. However, there may be some loss of formaldehyde, methanol, or other solvent as tanks and reactors are vented. Some formaldehyde, solvents, and alcohols are also evolved in the curing of paint films and the curing of adhesives and resins applied to textiles and paper. The amounts of material evolved in curing the resins may be small so that it may be difficult to justify the installation of complex recovery equipment. However, in the development of new resins for coatings and for treating textiles and paper, emphasis is being placed on those compositions that evolve a minimum of by-products on curing.

Uses

ADHESIVE RESINS

From antiquity, glues had been made almost entirely from materials of animal or vegetable origin, and were sensitive to moisture, oxidation, and bacterial or fungus attack. Because of these deficiencies, production of durable plywood, for example, was not possible. The modern plywood industry actually owes its growth to the availability of relatively low cost urea adhesives. Plywood and chipboard or wood chip glues are often made at the plywood and chip board mill.

Urea and melamine adhesives represent products of very mature and overaged technologies. Essentially, they are simple reaction products of urea or melamine with formaldehyde; they may be liquids or powders. Liquids are converted to dry powders by "spray drying." Melamine-urea combinations generally are spray-dried powders of co-reacted liquid melamine and urea-formaldehyde resins.

These adhesives are essentially for gluing wood. Urea–formaldehyde adhesives are used in the manufacture of plywood, in the fortification of starch

adhesives for manufacture of paper bags and corrugated box boards, the production of "floral" and insulating foams, high quality sandpaper, and parquet flooring. Large volumes of urea resins are also sold in the United States for particle board bonding and other uses, at relatively low prices.

Melamine or melamine–ureas are used in the manufacture of truck and railroad flooring, laminated lumber, beams, exterior doors, marine plywood, toilet seats, and school furniture. The bonds in these products meet a variety of commercial, military, and federal specifications for exterior waterproof adhesives.

Ureas modified with furfuryl alcohol [98-00-0] find excellent acceptance for gluing or assembly of furniture, sporting goods, eg, tennis rackets, fishing rods, and water skis, and for bonding decorative laminates to substrates such as particle board . Such ureas are called gap-filling adhesives. The modifier makes the resin less rigid, less highly cross-linked, and better able to relieve stresses imposed by shrinkage due to cure and loss of water in glue lines of nonuniform thickness.

In gluing, the adhesive must not saturate veneers or wood chips, but must remain in the glue line on the surface of the chips or between the plies. The adhesives are generally of high viscosity so that they remain in the glue line. Thickeners and extenders, such as powdered pecan shells and wheat flour, are often used.

Urea resin adhesives, by the use of the proper hardener, may be set either by heat or at room temperature. For room temperature curing, the hardener may be ammonium chloride, together with basic materials like calcium phosphate to neutralize excess acid that might damage the wood. Cold set or room temperature set adhesives are those that set satisfactorily at 20–30°C, whereas a hot set adhesive generally means one that is set above 99°C. Those that cure well between these temperatures are often referred to as intermediate set. Cold set types naturally set much faster at intermediate temperatures. Cold pressing of plywood is usually done in a hydraulic press. The press may then be opened, the clamped assembly removed and allowed to stay under the pressure of the clamps for at least four hours to set the glue.

Very rapid cures may be achieved by applying heat in the form of microwave radiation (see MICROWAVE TECHNOLOGY). The moist amino resin adhesive absorbs the high frequency radiation more readily than dry wood, thereby concentrating the heat in the glue line where it is needed. Hot pressing may be conducted in a hydraulic press comprising a large number of steam heated platens usually 5 cm thick. Pressures usually range from 1 –2 MPa (150–300 psi). Hot press temperatures for urea and melamine-urea are usually 115–132°C.

In plywood production with ureas, the spread veneers should be pressed as soon as possible. The time between spreading and pressing, usually called assembly time, should never exceed one hour. With some formulations, the permissible assembly time may be no longer than 15 minutes. Melamine formulations and uncatalyzed melamine–urea combinations, however, can be spread and stored for as much as a week before use.

Ureas are not satisfactory for prolonged water immersion or for continuous exposure to warm and excessively humid conditions, although they are fairly resistant to normal humidity. Somewhat more durable bonds are obtained by heat setting. Ureas can be extended with wheat or rye flour, using as much as 150 parts flour to 100 parts dry resin. The extended glue still retains a fair degree of moisture resistance. Melamine resins have excellent water resistance, but cannot be cured at room temperature. Durable laminated wood beams used in building construction usually employ microwave technology for heat curing.

Continuous production of urea–formaldehyde resins has been described in many patents. In a typical example, urea and formaldehyde are combined and the solution pumped through a multistage unit. Temperature and pH are controlled at each stage to achieve the appropriate degree of polymerization. The product is then concentrated in a continuous evaporator to about 60–65° solids (31).

LAMINATING RESINS

Phenolic and melamine resins are both used in the manufacture of decorative laminated plastic sheets for counters and table tops (see LAMINATES; REINFORCED PLASTICS). The phenolic is functional, being used in the backing or support sheets, whereas the melamine resin performs both decorative and functional roles in the print sheet and the protective overlay. Hardness, transparency, stain resistance, and freedom from discoloration are essential, in addition to a long-lasting working surface. Transparency is achieved because the refractive index of cured melamine–formaldehyde resin approaches that of the cellulose fibers and thus there is little scattering of light. Low cost and good mechanical properties are provided by the phenolic backing layers. In this instance, the combination of phenolic and amino resins achieves an objective that neither would normally be capable of performing alone. Developments in modified melamine resins have contributed to commercialization of premium priced through-color decorative laminates in which the dark color phenolic backing layers are replaced by color layers matching the full range of surface colors.

Phenolic resins are generally used in alcoholic solution, whereas melamine resins are best handled in water or water–alcohol mixtures. The paper or cloth web is passed through a dip tank containing resin solution, adjusted for pick-up on squeeze rolls, and then passed through a heated drying oven. Once dried, the treated paper or cloth is fairly stable and, stored in a cool place, it may be kept for several weeks or months before pressing into laminated plastic sheets.

A melamine laminating resin used to saturate the print and overlay papers of a typical decorative laminate might contain two moles of formaldehyde for each mole of melamine. In order to inhibit crystallization of methylol melamines, the reaction is continued until about one-fourth of the reaction product has been converted to low molecular weight polymer. A simple determination of free formaldehyde may be used to follow the first stage of the reaction, and the build-up of polymer in the reaction mixture may be followed by cloud-point dilution or viscosity tests.

A particularly interesting and useful test is run at high dilution. One or two drops of resin are added to a test tube half full of water. A cloudy streak as the drop sinks through the water indicates that the resin has advanced to the point where the highest molecular weight fraction of polymer is no longer soluble in water at that particular temperature. At this high dilution, the proportion of water to resin is not critical, hence the only measurement needed is the temperature of the water. The temperature at or below which the drops give a white streak is known as the hydrophobe temperature. This test is particularly useful with melamine resins.

Laminates are pressed in steam-heated, multiple-opening presses. Each opening may contain a book of as many as ten laminates pressed against polished steel plates. Curing conditions are 20–30 min at about 150°C under a pressure of about 6900 kPa (1000 psi).

MOLDING COMPOUNDS

Molding was the first big application for amino resins, although molding compounds are more complex than either laminating resins or adhesives. A simple amino resin molding compound might be made by combining melamine with 37° formalin in the ratio of two moles of formaldehyde for each mole of melamine at neutral or slightly alkaline pH and a temperature of 60°C. The reaction should be continued until some polymeric product has been formed to inhibit crystallization of dimethylolmelamine upon cooling. When the proper reaction stage has been reached, the resin syrup is pumped to a dough mixer where it is combined with alpha-cellulose pulp, approximately one part of cellulose to each three parts of resin solids. The wet, spongy mass formed in the dough mixer is then spread on trays where it is combined with alpha-cellulose in a humidity-controlled oven to produce a hard, brittle popcornlike intermediate. This material may be coarsely ground and sent to storage. To make the molding material, the cellulose-melamine resin intermediate is combined in a ball mill with a suitable catalyst, stabilizer, colorants, and mold lubricants. The materials must be ground for several hours to achieve the uniform fine dispersion needed to get the desired decorative appearance in the molded article. The molding compound may be used as a powder or it may be compacted under heat and pressure to a granular product that is easier to handle (32). A urea molding compound might be made in much the same way using a resin made with 1.3–1.5 mol of formaldehyde per 1.0 mol of urea.

Amino molding compounds can be compression, injection, or transfer molded. Urea molding compound has found wide use and acceptance in the electrical surface wiring device industry. Typical applications are circuit breakers, switches, wall plates, and duplex outlets. Urea is also used in closures, stove hardware, buttons, and small housings. Melamine molding compound is used primarily in dinnerware applications for both domestic and institutional use. It is also used in electrical wiring devices, ashtrays, buttons, and housings.

The emergence of a new amino application is rare at this point in its relatively long life, but one such has appeared and is growing rapidly. Because of

the relative hardness of both urea and melamine moldings, a unique use has been developed for small, granular sized particles of cut up molded articles. It is the employment of a pressurized stream of plastic particles to remove paint without damaging the surface beneath, and can be compared to a sandblasting operation. This procedure is gaining wide acceptance by both commercial airlines and the military for the refinishing of painted surfaces. It does not harm the substrate and eliminates the use of chemicals formerly used in stripping paint.

To speed up the molding process, the required amount of molding powder or granules is often pressed into a block and prewarmed before placing it in the mold. Rapid and uniform heating is accomplished in a high frequency preheater; essentially an industrial microwave oven. The prewarmed block is then transferred to the hot mold, pressed into shape, and cured.

Production of decorated melamine plastic dinner plates makes use of molding and laminating techniques. The pattern is printed on the same type of paper used for the protective overlay of decorative laminates, treated with melamine resin and dried, and then cut into disks of the appropriate size.

To make a decorated plate, the mold is opened shortly after the main charge of molding compound has been pressed into shape, the decorative foil is laid in the mold on top of the partially cured plate, printed side down, and the mold closed again to complete the curing process. The melamine-treated foil is thus fused to the molded plate and, as with the decorative laminate, the overlay becomes transparent so that the printed design shows through yet is protected by the film of cured resin.

The excellent electrical properties, hardness, heat resistance, and strength of melamine resins makes them useful for a variety of industrial applications. Some representative properties of amino resin molding compounds, including the industrial-grade melamines, are listed in Table 2.

Table 2. Typical Properties of Filled Amino Resin Molding Compounds

ASTM or UL test	Property	Urea	Melamine		
		Alpha-cellulose	Alpha-cellulose	Macerated fabric	Glass fiber
Physical					
D792	specific gravity	1.47–1.52	1.47–1.52	1.5	1.8–2.0
D570	water absorption, 24 h, 3.2 mm thick, %	0.48	0.1–0.6	0.3–0.6	0.09–0.21
Mechanical					
D638	tensile strength, MPa ^a	38–48	48–90	55–69	35–70
D638	elongation, %	0.5–1.0	0.6–0.9	0.6–0.8	
D638	tensile modulus, GPa ^b	9–9.7	9.3	9.7–11	16.5
D785	hardness, Rockwell M	110–120	120	120	115
D790	flexural strength, MPa ^a	70–124	83–104	83–104	90–165
D7900	flexural modulus, GPa ^b	9.7–10.3	7.6	9.7	16.5
D256	impact strength, J m ^c of notch	14–18	13–19	32–53	32–1000
Thermal					
C177	thermal conductivity, 10 ^{−4} W (m·K)	42.3	29.3–42.3	44.3	48.1
D696	coefficient of thermal expansion, 10 ^{−5} cm (cm·°C)	2.2–3.6	2.0–5.7	2.5–2.8	1.5–1.7
D648	deflection temperature at 1.8 MPa ^a , °C	130	182	154	204
UL 94	flammability class	VO ^d	VO ^d		VO
	continuous no-load service temperature, °C	77 ^e	99 ^e	121	149–204
Electrical					
D149	dielectric strength, V 0.00254 cm short time, 3.2 mm thick	330–370	270–300	250–350	170–300
	step by step	220–250	240–270	200–300	170–240
D150	dielectric constant, 22.8°C				
	at 60 Hz	7.7–7.9	8.4–9.4	7.6–12.6	9.7–11.1
	at 10 ³ Hz		7.8–9.2	7.1–7.8	
D150	dissipation factor, 22.8°C				
	at 60 Hz	0.034–0.043	0.030–0.083	0.07–0.34	0.14–0.23
	at 10 ³ Hz		0.015–0.036	0.03–0.05	
D257	volume resistivity, 22.8°C, 50% rh, ohm·cm	0.5–5.0 × 10 ¹¹	0.8–2.0 × 10 ¹²	1.0–3.0 × 10 ¹¹	0.9–2.0 × 10 ¹¹
D495	arc resistance, s	80–100	125–136	122–128	180–186

^a To convert MPa to psi, multiply by 145.
^b To convert GPa to psi, multiply by 145,000.
^c To convert J m to ftlbf in., divide by 53.38.
^d Applies to specimens thicker than 1.6 mm.
^e Based on no color change.

In 1989 quantity costs, which reflect the lowest cost, of urea molding compounds, were approximately \$1.41 kg (\$0.035 in.³) for black and brown colors, \$1.58 kg (\$0.039 in.³) for white and ivory; special colors are somewhat higher in price. The approximate cost of cellulose-filled melamine molding compound is \$1.74 kg (\$0.043 in.³). Glass fiber-filled melamine sells for \$7.70 kg (\$0.22 in.³). Amino molding compounds are produced worldwide. The following list represents the major suppliers.

Company	Location	Product
American Cyanamid	USA	urea melamine
BIP Chemical	England	urea melamine
Budd Chemical	USA	urea
Carmel Chemical	Israel	urea melamine
Fiberite	USA	melamine
Perstrop	Sweden USA	urea melamine

Plastics Mfg. Co.	USA	urea
Plastics Engineering Co.	USA	melamine melamine

COATINGS

Cured amino resins are far too brittle to be used alone as surface coatings for metal or wood substrates, but in combination with other film formers (alkyds, polyesters, acrylics, epoxies) a wide range of acceptable performance properties can be achieved. These combination binder coating formulations cure rapidly at slightly elevated temperatures, making them well suited for industrial baking applications. The amino resin content in the formulation is typically in the range of 10–50% of the total binder solids.

A wide selection of amino resin compositions is commercially available. They are all alkylated to some extent in order to provide compatibility with the other film formers, and formulation stability. They vary not only in the type of amine (melamine, urea, benzoguanamine, and glycoluril) used, but also in the concentration of combined formaldehyde, and the type and concentration of alkylation alcohol (*n*-butanol, isobutyl alcohol, methanol).

On curing, amino resins not only react with the nucleophilic sites (hydroxyl, carboxyl, amide) on the other film formers in the formulation, but also self-condense to some extent. Highly alkylated amino resins have less tendency to self-condense (33,34) and are therefore effective cross-linking agents, but may require the addition of a strong acid catalyst to obtain acceptable cure even at bake temperatures of 120–177°C.

Amino resins based on urea have advantages in low temperature cure response and low cost. However, they are not as stable to ultraviolet (uv) radiation as melamine resins, and have poorer heat resistance; therefore, they have been successful primarily in interior wood finishes. Melamine resins, on the other hand, are ultraviolet stable, have excellent heat resistance, film hardness, and chemical resistance. They therefore dominate amino resin usage in OEM automotive coatings, general metals finishes, container coatings (both interior and exterior), and prefinished metal applications. Glycoluril resins have also found use in prefinished metal, primarily because of their high film flexibility properties. Unalkylated glycoluril resins are unique in that they are stable under slightly acidic conditions and have therefore found use in low temperature cure waterborne finishes. Benzoguanamine resins have historically been successful in appliance finishes because of their superior chemical resistance and specifically their detergent resistance. However, they have both poor ultraviolet resistance and economics, which have limited their use in other application areas.

When first introduced to the coatings industry, amino resin compositions were partially butylated and relatively polymeric in nature, with degrees of polymerization of 4–6. However, the dominant amino resin in today's industrial coating is based on a highly methylated, highly monomeric (degrees of polymerization of 1.4–2.6) melamine cross-linking agent. Variations of extent of methylolation and methylation exist along with a number of co-ethers where the melamine molecule is both methylated and either *n*-butylated or iso-butylated. This type of composition dominates because it best addresses the pollution (low volatile organic compounds) and performance requirements of today's industrial finishes (see COATINGS, INDUSTRIAL).

Methylation provides fast cure response, improved exterior exposure, high weight retention on curing, and suitability for both solvent and waterborne systems. Waterborne systems, in most instances, provide lower pollution than solvent-based formulations. High monomer content reduces the viscosity of the amino resin, again lowering pollution particularly when used in solvent-based systems, and also improves film flexibility, and recoat adhesion. When some butylation is included as part of the alkylation, the viscosity of the amino resin is lowered, thereby lowering pollution (of the formulated coating), improving recoat adhesion, and improving wetting and flow characteristics. An amino resin is usually selected based on specific performance properties required or performance to be emphasized.

Stability in storage is an important property for coating systems containing amino resins. If the amino resin undergoes self-condensation or reacts at room temperature with the alkyd or other film-forming polymer, the system may become too viscous or thicken to a gel which can no longer be used for coating. Alkyds usually contain sufficient free carboxyl groups to catalyze the curing reaction when the coating is baked, but this may also cause the paint to thicken in storage. Partial neutralization of the acid groups with an amine can greatly improve storage stability yet allow the film to cure when baked, since much of the amine is vaporized with the solvent during the baking process. 2-Amino-2-methyl-1-propanol [124-68-5], triethylamine [121-44-8], and dimethylaminoethanol [108-01-1] are commonly used as stabilizers. Alcohols as solvent also improve storage stability. Catalyst addition just before the coating is to be applied permits rapid curing and avoids the problem of storage stability. A strong acid soluble in organic solvents such as *p*-toluenesulfonic acid is very effective and may be partially neutralized with an amine to avoid premature reaction.

A butylated urea–formaldehyde resin for use in the formulation of fast-curing baking enamels might be made beginning with the charge: urea (1.0 mol), paraformaldehyde (2.12 mol), and butanol (1.50 mol). Triethanolamine is added to make the solution alkaline (about 1% of the weight of the urea) and the mixture is refluxed until the paraformaldehyde is dissolved. Phthalic anhydride is added to give a pH of 4.0 and the water removed by azeotropic distillation until the batch temperature reaches 117°C. Cooling and dilution with solvent is done until the desired solids content is reached (35).

A highly methylated melamine–formaldehyde resin for cross-linking with little or no self-condensation might be made as follows (36). A solution of formaldehyde in methyl alcohol is charged to a reaction kettle and adjusted to a pH of 9.0–9.5 using sodium hydroxide. Melamine is then added to give a ratio of 1 mol of melamine for each 6.5 mol of formaldehyde and the mixture refluxed for one-half hour. The reaction is then cooled to 35°C and more methanol added to bring the ratio of methanol per mole of melamine up to 11. With the batch temperature at 35°C, enough sulfuric acid is added to reduce the pH to 1.0. After holding the reaction mixture at this temperature and pH for 1 h, the batch is neutralized with 50% sodium hydroxide and the excess methanol stripped to give a product containing 60% solids which is then clarified by filtration. A highly methylated resin, such as this, may be used in water-based (37) or solvent-type coatings. It might also be used to provide crease resistance to cotton fabric.

The principal problems facing amino resins in the industrial coatings of the 1990s are formaldehyde emission and low temperature cure performance. Significant progress has been made in reducing the residual free formaldehyde in the amino resin, but formaldehyde generation on baking must still be addressed. Concerning low temperature cure performance, emphasis is being placed on catalyst selection. Amino resins cure at bake temperatures as low as 71–82°C, but at these bake temperatures they require high concentrations of acid catalyst, which negatively affect hydrolysis resistance or water sensitivity of the cured film. The development of improved catalysts is the most promising solution to low temperature cure performance enhancement.

TEXTILE FINISHES

Most amino resins used commercially for finishing textile fabrics are methylolated derivatives of urea or melamine. Although these products are usually monomeric, they may contain some polymer by-product.

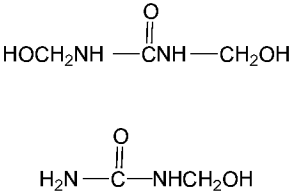
Amino resins react with cellulosic fibers and change their physical properties. They do not react with synthetic fibers, such as nylon, polyester, or acrylics, but may self-condense on the surface. This results in a change in the stiffness or resiliency of the fiber. Partially polymerized amino resins of such molecular size that prevents them from penetrating the amorphous portion of cellulose also tend to increase the stiffness or resiliency of cellulose fibers.

Monomeric amino resins react predominantly with the primary hydroxyls of the cellulose, thereby replacing weak hydrogen bonds with strong covalent bonds which leads to an increase in fiber elasticity. When an untreated cotton fiber is stretched or deformed by bending, as in forming a crease or wrinkle, the relatively weak hydrogen bonds are broken and then reform to hold the fiber in its new position. The covalent bonds that are formed when adjacent cellulose chains are cross-linked with an amino resin are five to six times stronger than the hydrogen bonds. Covalent bonds are not broken when the fiber is stretched or otherwise deformed. Consequently, the fiber tends to return to its original condition when the strain is removed. This increased elasticity is manifested in two important ways: (1) When a cotton fabric is cross-linked while it is held flat, the fabric tends to return to its flat condition after it has been wrinkled during use or during laundering. Garments made from this type of fabric are known as wash-and-wear, minimum care, or no-iron. (2) A pair of pants that is pressed to form a crease and then cross-linked tends to maintain the crease through wearing and laundering. This type of garment is called durable-press or permanent press (see TEXTILES).

This increased elasticity is always accompanied by a decrease in strength of the cellulose fiber which occurs even though weak hydrogen bonds are replaced by stronger covalent bonds. The loss of strength is not caused by hydrolytic damage to the cellulose. If the cross-linking agent is removed by acid hydrolysis, eg, the fiber will regain most, if not all, of its original strength. The loss in strength is believed to be due to intramolecular reaction of the amino resin along the cellulose chain to displace a larger number of hydrogen bonds, resulting in a net loss in strength. The intramolecular and intermolecular reactions (cross-linking) both occur at the same time.

Although there are many different amino resins used for textile finishing, all of them impart about the same degree of increase in elasticity when applied on an equal molar basis. Elasticity can be measured by determining the recovery from wrinkling. Although all these products impart about the same degree of improvement in elasticity, they also may impart many other desirable or undesirable properties to the fabric. The development of amino resins for textile finishing has been aimed toward maximizing the desirable properties and minimizing the undesirable ones. Most of the resins and reactants used in today's textile market are based on urea as a starting material. However, the chemistry differs considerably from that employed in early textile-finishing operations.

The first amino resins used commercially on textiles were the so-called urea –formaldehyde resins, dimethylolurea [140-95-4], or its mixtures with monomethylolurea [1000-82-4].



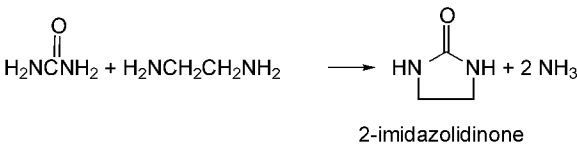
Their performance falls short of most present finishes, particularly in durability, resistance to chlorine-containing bleaches, and formaldehyde release, and they are not used much today. Both urea and formaldehyde are relatively inexpensive, and manufacture is simple; ie, 1–2 mol of formaldehyde as an aqueous solution reacts with 1 mol of urea under mildly alkaline conditions at slightly elevated temperatures.

Since the methylolurea monomers have limited water solubility (about 30%), they were usually marketed in dispersed form as soft pastes containing 55–65% active ingredient in order to decrease container and shipping costs. By increasing the temperature and using slightly acid conditions, dimethylolureas can be made as a series of short polymers that have infinite water solubility and can be marketed at concentrations as high as 85%. However, because these result in increased fabric stiffness, they cannot be used interchangeably with the monomeric materials. Both forms polymerize readily in storage and, unless kept under refrigeration, become water insoluble within a few weeks at ambient temperatures.

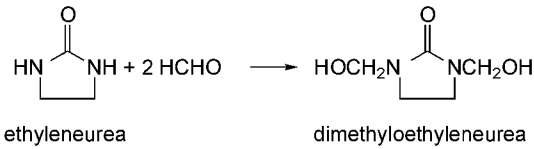
To overcome stability and water solubility problems, methylolurea resins are frequently alkylated to block the reactive hydroxyl groups. For reasons of economy the alkylating agent is usually methanol. In this process, 2 mol of aqueous formaldehyde reacts with 1 mol of urea under alkaline conditions to form dimethylolurea. Excess methanol is then added, and the reaction continued under acid conditions to form methoxymethylurea. Both methylol groups can be methylated by maintaining low concentrations of water and using a large excess of methanol; however, methylation of only one of the methylol groups is sufficient to provide adequate shelf life and water solubility. Upon completion of the methylation reaction, the resin is adjusted to pH 7–10, and excess methanol and water are removed by distillation under reduced pressure to provide syrups of 50–80% active ingredients.

Like methylolureas, cyclic ureas are based on reactions between urea and formaldehyde; however, the amino resin is cyclic rather than linear. Many cyclic urea resins have been used in textile-finishing processes, particularly to achieve wrinkle resistance and shrinkage control, but the ones described below are the most commercially important. They are all in use today to greater or lesser extents, depending on specific end requirements (see also TEXTILES, FINISHING).

Ethyleneurea Resins. One of the most widely used resins during the 1950s and 1960s was based on dimethylolethyleneurea [136-84-5] (1,3-bis(hydroxymethyl)-2-imidazolidinone) commonly known as ethyleneurea resin. This resin [28906-87-8] is most conveniently prepared from urea, ethylenediamine, and formaldehyde. 2-Imidazolidinone [120-93-4] (ethyleneurea) is first prepared by the reaction of excess ethylenediamine [107-15-3] with urea (38) in an aqueous medium at about 116°C.

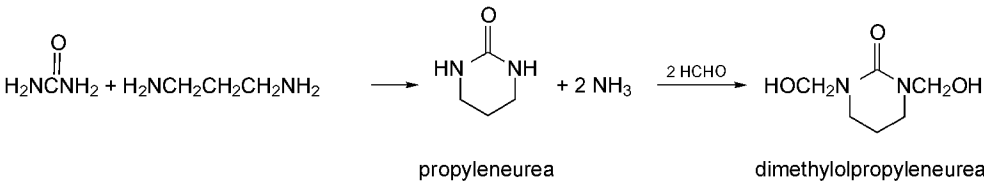


A fractionating column is required for the removal of ammonia and recycle of ethylenediamine. The molten product (mp 133°C) is then run into ice water to give a solution that is methylolated with 37% aqueous formaldehyde.



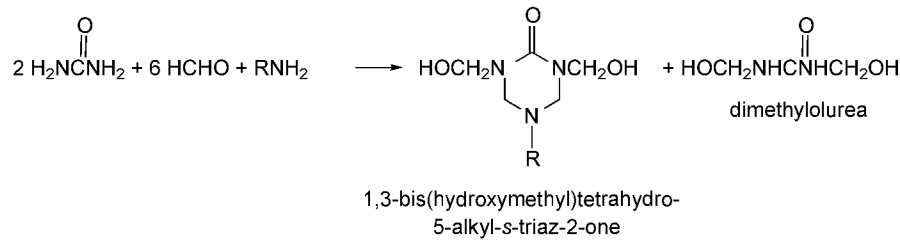
The resin, generally a 50% solution in water, has excellent shelf life and is stable to hydrolysis and polymerization.

Propylene Urea Resins. In similar fashion to ethyleneurea, dimethyl-olpropyleneurea [3270-74-4] [1,3-bis(hydroxymethyl)tetrahydro-2-(1*H*)-pyrimidinone] is the basis of propyleneurea–formaldehyde resin [65405-39-2]. Its preparation is from urea, 1,3-diaminopropane [109-76-2], and formaldehyde.



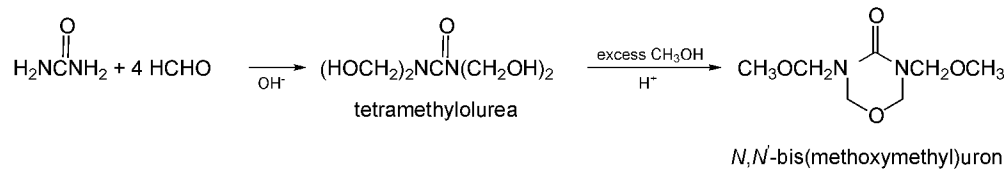
This resin was temporarily accepted, primarily because of its improved resistance to acid washes. However, the relatively high cost of the diamine precluded widespread commercial acceptance.

Triazone. Triazone is the common name for the class of compounds corresponding to the dimethylol derivatives of tetrahydro-5-alkyl-*s*-triazone. They can be made readily and cheaply from urea, formaldehyde, and a primary aliphatic amine. A wide variety of amines may be used to form the six-membered ring (39); however, for reasons of cost and odor, hydroxyethylamine (monoethanolamine) is used preferentially (see ALKANOLAMINES). Since the presence of straight-chain methylolureas causes no deleterious effects to the fabric finish, the triazones typically are prepared with less than the stoichiometric quantity of the amine. This results not only in a less costly resin but also in improved performance (40).

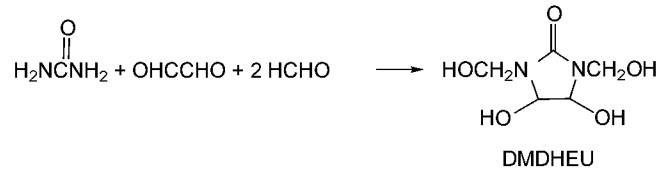


The resin is simply prepared by heating the components together. Usually the urea and formaldehyde are first charged to the kettle and heated under alkaline conditions to give a mixture of polymethylolureas, followed by the slow addition of the amine with continued heating to form the cyclic compound. The order of addition can be varied as can the molar ratios to yield a range of chain-ring compound ratios. The commercial resin is usually sold as a 50% solids solution in water.

Uron Resins. In the textile industry, the term uron resin usually refers to the mixture of a minor amount of melamine resin and so-called uron, which in turn is predominantly *N,N'*-bis(methoxymethyl)uron [7388-44-5] plus 15–25% methylated urea–formaldehyde resins, a by-product. *N,N'*-bis(methoxymethyl)uron was first isolated and described in 1936 (41), but was commercialized only in 1960. It is manufactured (42) by the reaction of 4 mol of formaldehyde with 1 mol of urea at 60°C under highly alkaline conditions to form tetramethylolurea [2787-01-1]. After concentration under reduced pressure to remove water, excess methanol is charged and the reaction continued under acidic conditions at ambient temperatures to close the ring and methylate the hydroxymethyl groups. After filtration to remove the precipitated salts, the methanolic solution is concentrated to recover excess methanol. The product (75–85% pure) is then mixed with a methylated melamine–formaldehyde resin to reduce fabric strength losses in the presence of chlorine, and diluted with water to 50–75% solids. Uron resins do not find significant use today due to the greater amounts of formaldehyde released from fabric treated with these resins.

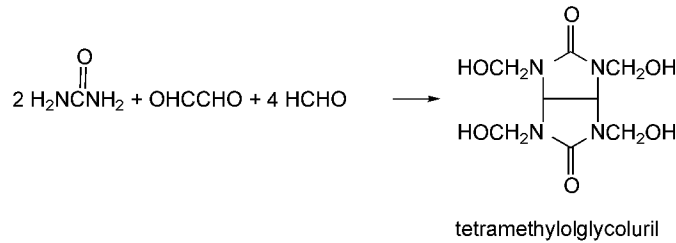


Glyoxal Resins. Since the late 1960s, glyoxal resins have dominated the textile-finish market for use as wrinkle-recovery, wash-and-wear, and durable-press agents. These resins are based on 1,3-bis(hydroxymethyl)-4,5-dihydroxy-2-imidazolidinone, commonly called dimethyloldihydroxyethyleneurea [1854-26-8] (DMDHEU). Several methods of preparation are described in the literature (43). On a commercial scale, DMDHEU can be prepared inexpensively at high purity by a one-kettle process (44): 1 mol of urea, 1 mol of glyoxal [107-22-2] as 40% solution, and 2 mol of formaldehyde in aqueous solution are charged to the reaction vessel. The pH is adjusted to 7.5–9.5 and the mixture heated at 60–70°C. The reaction is nearly stoichiometric; excess reagent is not necessary.



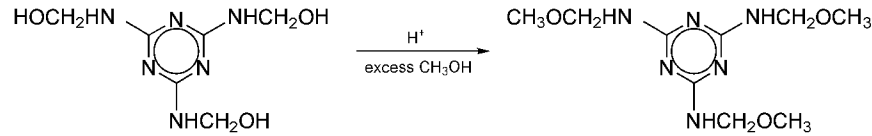
Glyoxal resins are generally sold at 45% solids solutions in water. Resin usage for crease-resistant fabrics had increased to well over 60 × 10⁶ kg by 1974 and over half of this was DMDHEU for durable-press garments. In the early 1980s glyoxal resins modified with diethylene glycol [111-46-6] became prominent in the marketplace. These products are either simple mixtures of diethylene glycol and DMDHEU in water solution or the reaction product of diethylene glycol and DMDHEU. Rarely, ethylene glycol has been used in place of diethylene glycol. The diethylene glycol modified DMDHEU products have the advantage of releasing significantly less formaldehyde from the finished fabric after resin curing than fabric treated with DMDHEU. On the other hand, durable-press performance and shrinkage control are somewhat less with the glycol modified resins.

A less important glyoxal resin is tetramethylolglycoluril [5395-50-6] (tetramethylolacetylenediurea) produced by the reaction of 1 mol of glyoxal with 2 mol of urea, and 4 mol of formaldehyde.



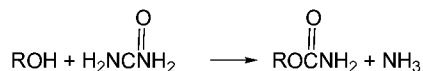
This resin was most popular in Europe, partly because of its lower requirements of glyoxal. However, because of increased availability and lower glyoxal costs plus certain application weaknesses, it has been generally replaced by DMDHEU.

Melamine–Formaldehyde Resins. The most versatile textile-finishing resins are the melamine–formaldehyde resins. They provide wash-and-wear properties to cellulosic fabrics, and enhance the wash durability of flame-retardant finishes. Butylated melamine–formaldehyde resins of the type used in surface coatings may be used in textile printing-ink formulations. A typical textile melamine resin is the dimethyl ether of trimethylolmelamine [1852-22-8] which can be prepared as follows:



Under alkaline conditions, 3 mol of formaldehyde react with 1 mol of melamine at elevated temperatures. Since water interferes with the methylation, methylation is carried out in methanol with paraformaldehyde and by simply adjusting the pH to about 4 with continued heating. After alkylation is complete the pH is adjusted to 8–10 and excess methanol is distilled under reduced pressure. The resulting syrup contains about 80% solids.

Miscellaneous Resins. Much less important than the melamine–formaldehyde and urea–formaldehyde resins are the methylol carbamates. They are urea derivatives since they are made from urea and an alcohol (R can vary from methyl to a monoalkyl ether of ethylene glycol).



Temperatures in excess of 140°C are required to complete the reaction and pressurized equipment is used for alcohols boiling below this temperature; provision must be made for venting ammonia without loss of alcohol. The reaction is straightforward and, in the case of the monomethyl ether of ethylene glycol [109-86-4], can be carried out at atmospheric pressure using stoichiometric quantities of urea and alcohol (45). Methylolation with aqueous formaldehyde is carried out at 70–90°C under alkaline conditions. The excess formaldehyde needed for complete dimethylolation remains in the resin and prevents more extensive usage because of formaldehyde odor problems in the mill.

Other amino resins used in the textile industry for rather specific properties have included the methylol derivatives of acrylamide (46), hydantoin [461-79-3] (47), and dicyandiamide (48).

Textiles are finished with amino resins in four steps. The fabric is (1) passed through a solution containing the chemicals, (2) through squeeze rolls (padding) to remove excess solution, (3) dried, and (4) heated (cured) to bond the chemicals with the cellulose or to polymerize them on the fabric surface.

The solution (pad bath) contains one or more of the amino resins described above, a catalyst, and other additives such as a softener, a stiffening agent, or a water repellent. The catalyst may be an ammonium or metal salt, eg, magnesium chloride or zinc nitrate. Synthetic fabrics, such as nylon or polyester, are treated with amino resins to obtain a stiff finish. Cotton (qv) or rayon fabrics or blends with synthetic fibers are treated with amino resins to obtain shrinkage control and a durable-press finish.

Normally, fabrics are treated in the sequence outlined above. The temperature of the drying unit is 100–110°C and the temperature of the curing unit can vary between 120 and 200°C but usually ranges from 150 to 180°C. The higher temperatures are employed to polymerize the resins on synthetic fabrics and at the same time to heat-set the fibers. Temperatures up to 180°C are used to allow the amino resins to react with cellulosic fibers alone or blended with synthetic fibers. The fabric is held flat but with minimum tension during drying and curing and always tends to become flat when creased or wrinkled during use or laundering. The resin-treated cellulose absorbs less water and swells less than untreated cellulose. This reduced swelling along with little or no tension induced during drying minimizes shrinkage during laundering.

The steps followed in the precure are repeated in the postcure process, except that after the drying step the goods are shipped to a garment manufacturer who makes garments, presses them into the desired shape with creases or pleats, and then cures the amino resin on the completed garment. It is important that the amino resins used in the postcure process should (1) not react with the fabric before it has been fashioned into a garment, and (2) release a minimum amount of formaldehyde into the atmosphere, especially while the goods are in storage or during the cutting and sewing operations. These requirements are met, at present, with the diethylene glycol modified DMDHEU resin.

Tire Cord. Melamine resins are also used to improve the adhesion of rubber to reinforcing cord in tires. Textile cord is normally coated with a latex dip solution composed of a vinylpyridine–styrene–butadiene latex rubber containing resorcinol–formaldehyde resin. The dip coat is cured prior to use. The dip coat improves the adhesion of the textile cord to rubber. Further improvement in adhesion is provided by adding resorcinol and hexa(methoxymethyl) melamine [3089-11-0] (HMMM) to the rubber compound which is in contact with the textile cord. The HMMM resin and resorcinol cross-link during rubber vulcanization and cure to form an interpenetrating polymer within the rubber matrix which strengthens or reinforces the rubber and increases adhesion to the textile cord. Brass-coated steel cord is also widely used in tires for reinforcement. Steel belts and bead wire are common applications. Again, HMMM resins and resorcinol [108-46-3] are used in the rubber compound which is in contact with the steel cord to reinforce the rubber and increase the adhesion of the rubber to the steel cord. This use of melamine resins is described in the patent literature (49).

AMINO RESINS IN THE PAPER INDUSTRY

Paper (qv) is a material of tremendous versatility and utility, prepared from a renewable resource. It may be made soft or stiff, dense or porous, absorbent or water repellent, textured or smooth. Some of the versatility originates with the fibers, which may vary from short and supple to long and stiff, but the contribution of chemicals should not be underestimated (see PAPERMAKING MATERIALS AND ADDITIVES).

Amino resins are used by the paper industry in large volume for a variety of applications. The resins are divided into two classes according to the mode of application. Resins added to the fiber slurry before the sheet is formed are called wet-end additives and are used to improve wet and dry strength and stiffness. Resins applied to the surface of formed paper or board, almost invariably together with other additives, are used to improve the water resistance of coatings, the sag resistance in ceiling tiles, and the scuff resistance in cartons and labels.

The requirements for the two types of resins are very different. Wet-end additives are used in dilute fiber slurries in small amounts. After the sheet is formed, most of the water is drained away and some of the remaining water is pressed out of the sheet before it is dried. The amino resin must be retained (absorbed) on the surface of the cellulose fibers so that it will not be washed away. On a typical paper machine, fiber concentration in the headbox would be about 1%. If the amount of wet-strength resin used is 1% of the weight of the fiber, the concentration of resin in the headbox would be only 0.01%. If no mechanism for attaching the resin to the fiber is provided, only a trace of the resin added to the slurry would be retained in the finished sheet. Good retention is achieved with the amino resin by making the resin cationic. Since the cellulose surface is anionic because of the carboxylic acid groups present, the cationic charge on the resin makes it substantive with the fiber leading to good retention of the resin when applied in the wet-end. Resins for application to the surface of preformed paper are not required to be substantive to cellulose and they may be formulated for adhesion, cure rate, viscosity, compatibility with other materials, etc, without concern for retention.

The integrity of a paper sheet is dependent on the hydrogen bonds which form between the fine structures of cellulose fibers during the pressing and drying operations (see CELLULOSE). The bonds between hydroxyls of neighboring fibers are very strong when the paper is dry but are severely weakened as soon as the paper becomes wet. Bonding between the hydroxyls of cellulose and water is as energetic as bonding between two cellulose hydroxyls. As a consequence, ordinary paper loses most of its strength when it is wet or exposed to very high humidity. The sheet loses its stiffness and bursting, tensile, and tearing strength.

Many materials have been used over the years in an effort to correct this weakness in paper. If water can be prevented from reaching the sites of the bonding by sizing or coating the sheet, then a measure of wet strength may be attained. Water molecules are so small and cellulose so hydrophilic that this solution usually affords only temporary protection. Formaldehyde, glyoxal, polyethylenimine, and, more recently, derivatized starch (50) and derivatized cationic polyacrylamide resins (51) have been used to provide temporary wet strength. The first two materials must be applied to the formed paper but the other examples are substantive to the fiber and may be used as wet-end additives. Carboxymethyl-cellulose–calcium chloride and locust bean gum–borax are examples of two-component systems applied separately to paper that were used to a limited extent before the advent of the amino resins. Today three major types of wet-strength resins are used in papermaking: polyamide–polyamine resins cross-linked with epichlorohydrin (52) are used in neutral to alkaline papers; cationic polyacrylamide resins cross-linked with glyoxal are used for acid to neutral papers; and melamine–formaldehyde resins are used for acid papers.

During the thirty year period following the introduction of synthetic wet-strength additives to papermaking in 1942, most paper was made at acid pH. Low molecular weight (or even monomeric) trimethylolmelamine [1017-56-7], when dissolved in the proper amount of dilute acid and aged, polymerizes to a colloidal polymer that is retained well by almost all types of papermaking fiber, and produces high wet strength under the mild curing conditions easily attained on a paper machine (53,54). This resin, introduced by American Cyanamid in 1942, is still extensively used when rapid cure, high wet strength, and good dry strength are important in acid paper. Some processing improvements have been made, including a report (55) describing the formation of a stable melamine resin acid colloid using formic and phosphoric acids. The chemistry of this reaction is quite interesting.

Melamine–formaldehyde acts as an amine when dissolved in dilute acid, usually hydrochloric acid (HCl). During polymerization, between 20–80

monomeric units combine to form a polymer of colloidal dimensions (6–30 nm) with the elimination of water and HCl (56,57). The development of cationicity is associated with the loss of HCl, since a unit of charge on the polymer is generated for every mole of acid lost, and the pH decreases steadily during the polymerization. In a typical formulation at 12° solids at room temperature, polymerization is complete in about 3 h. The initially colorless solution develops a light blue haze and shows a strong Tyndall effect.

Such a colloidal sol is highly substantive to all papermaking fibers, kraft, sulfite, groundwood, and soda. For its successful use in paper mills, the pH must be kept low, both to prevent precipitation of the resin in an unusable form and to promote curing of the resin; and the concentration of sulfates in the white water on the paper machine must not be allowed to exceed 100 ppm, again because the resin is precipitated in an inactive form by high concentrations of sulfates. High sulfate concentrations may build up in mills using large amounts of alum for setting size or sulfuric acid for controlling pH.

The problem of sulfate sensitivity was solved by adding formaldehyde to the aged colloid which improved wet-strength efficiency and reduced sensitivity to sulfates (58). Later, equivalent results were obtained by adding the extra formaldehyde before the colloid was aged. The additional formaldehyde acts like an acid during the aging process and, unless compensated for by a reduction in the amount of acid charged, lowers the pH to a point where polymerization to the colloids is inhibited. The high efficiency (HE) resins have been used in mills with sulfate concentrations so high that use of regular trimethylolmelamine (MF₃) colloids would be uneconomical. Sulfate tolerance is a function of the amount of extra formaldehyde present. For best cost-performance, a family of HE colloids is necessary with composition varying from MF₄, for moderate sulfate concentrations, to MF₉, for very high sulfates.

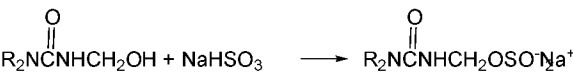
Formulations for regular and HE colloids are shown in Table 3 (59). The materials are added in the order listed to a 454 L (120 gal) tank provided with good agitation and ventilation. Formaldehyde fumes are evolved even from the regular colloid. The colloids develop only after aging and freshly prepared solutions are ineffective for producing wet strength. Stability of the colloids depends on temperature and concentration. Colloids at 10–12° are stable at room temperature for at least a week; stability may be extended by dilution after the colloids have aged properly.

Table 3. Formulations for Regular and HE Colloid Resins

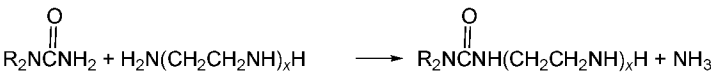
	Regular, MF ₃	HE MF ₈
water, 20° ± 10° C, kg	412.0	330.8
HCl, 20° Bñ, kg (1.16 g ml.), kg	17.7	14.1
formaldehyde, 37° o, kg		84.8
trimethylolmelamine, kg	45.4	45.4
Total	475.1	475.1

Both regular and HE colloids increase the wet strength of paper primarily by increasing adhesion between fibers; the strength of the individual fiber itself is unaffected (60). The resin appears to improve the adhesion between the fibers, whether they are wet or dry, by forming bonds that are unaffected by water. The excess formaldehyde in the HE colloid appears to function by increasing the amount of formaldehyde bound in the colloid (59). The regular colloid, starting with about 3 mol of formaldehyde per 1 mol of melamine, has about 2 mol bound in the colloid and 1 mol free. By mass action, the additional formaldehyde increases the amount of bound formaldehyde in the colloid. When an HE colloid is dialyzed or stored at very low concentrations (0.05° o), it loses the extra bound formaldehyde and behaves as a regular colloid.

The first urea–formaldehyde resins used to any extent as wet-strength agents were anionic polymers made by the reaction of a urea resin with sodium bisulfite (61). Attempts to use nonionic urea–formaldehyde polymers were unsuccessful; the neutral charge on the polymer made it unsubstantive to fiber resulting in lack of retention. The sulfomethyl group introduced by reaction with NaHSO₃ gave the polymers strong anionicity but substantivity was largely restricted to unbleached kraft pulp. Lignin residues probably provided sites for absorption of the polymer. The use of alum as a mordant was essential, since both the resin and the fiber were anionic. The reaction of bisulfite with the urea–formaldehyde polymer may be represented as:



In 1945, cationic urea resins were introduced and quickly supplanted the anionic resins, since they could be used with any type of pulp (62). Although they have now become commodities, their use in the industry has been steadily declining as the shift towards neutral and alkaline papermaking continues. They are commonly made by the reaction of urea and formaldehyde with one or more polyethylene–polyamines. The structure of these resins is very complicated and has not been determined. Ammonia is evolved during the reaction, probably according to the following:



Formaldehyde may react with the active hydrogens on both the urea and amine groups and therefore the polymer is probably highly branched. The amount of formaldehyde (2–4 mol per 1 mol urea), the amount and kind of polyamine (10–15° o), and resin concentration are variable and hundreds of patents have been issued throughout the world. Generally, the urea, formaldehyde, polyamine, and water react at 80–100°C. The reaction may be carried out in two steps with an initial methylation at alkaline pH, followed by condensation to the desired degree at acidic pH, or the entire reaction may be carried out under acidic conditions (63). The product is generally a syrup with 25–35° solids and is stable for up to three months.

The cationic urea resins are added to paper pulp preferably after all major refining operations have taken place. The pH on the paper machine must be acidic for reasonable rates of cure of the resin. Urea resins do not cure as rapidly as melamine–formaldehyde resins and the wet strength produced is not as resistant to hydrolysis. Furthermore, the resins are not retained as well as the melamine resins. On a resin-retained basis, however, their efficiency is as good. The lower retention of the urea–formaldehyde resins is due to their polydisperse molecular weight distribution. High molecular weight species are strongly absorbed on the fibers and are large enough to bridge two fibers. Low molecular weight species are not retained as well because of fewer charge sites. Attempts to improve the performance of urea–formaldehyde resins by fractionating the syrups by salt or solvent precipitation, or selective freezing or dialysis have been technically successful but economically impractical. The process for production of resins is sufficiently simple so that some paper mills have set up their own production units. With captive production, resins with higher molecular weights and lower stability may be tolerated.

The recovery of fiber from broke (off-specification paper or trim produced in the paper mill) is complicated by high levels of urea–formaldehyde and melamine–formaldehyde wet-strength resin. The urea resins present a lesser problem than the melamine resins because they cure slower and are not as resistant to hydrolysis. Broke from either resin treatment may be reclaimed by hot acidic repulping. Even the melamine resin is hydrolyzed rapidly under acidic conditions at high temperature. The cellulose is far more resistant and is not harmed if the acid is neutralized as soon as repulping is complete.

The TAPPI monograph (64) is an excellent source of additional information on technical and economic aspects of wet strength. An informative overview of the chemistry and mechanisms involved in wet strength chemistry can be found in reference 65.

Wet-strength applications account for the majority of amino resin sales to the paper industry but substantial volumes are sold for coating applications. The largest use is to improve the resistance of starch-clay coatings to dampness. In offset printing, which is becoming ever more important in the graphic arts, the printing paper is exposed to both ink and water. If the coating lifts from the paper and transfers to the plate, it causes smears and forces a shutdown for cleaning. A wide variety of materials have been added to the coatings to improve wet-rub resistance, including casein, soya protein,

poly(vinyl acetate), styrene–butadiene latices, glyoxal–urea resins and amino resins. Paper coatings are applied at as high a solids content as possible to ease the problem of drying. Retention is not a problem since the resin is applied to a preformed sheet. The important characteristics for coating resins are high solids at low viscosity, high cure rates, and high wet-rub efficiency. Urea and melamine resins or mixtures are sold as high solids syrups or dry powders. They are used with starch–pigment coatings with acidic catalysts or with starch–pigment–casein (or protein) coatings usually without catalysts. The syrups are frequently methylated for solubility and stability at high solids. All of the resins are of intrinsically low molecular weight to reduce viscosity for ease of handling (see COATINGS, INDUSTRIAL).

Closely allied to resins for treating paper are the resins used to treat regenerated cellulose film (cellophane) which does not have good water resistance unless it is coated with nitrocellulose or poly(vinylidene chloride). Adhesion of the waterproofing coating to the cellophane film is achieved by first treating the cellophane with an amino resin. The cellophane film is passed through a dip tank containing about 1% of a melamine–formaldehyde acid colloid type of resin. Some glycerol may also be present in the resin solution to act as a plasticizer. Resins for this purpose are referred to as anchoring agents.

OTHER USES

Water-soluble melamine–formaldehyde resins are used in the tanning of leather in combination with the usual tanning agents (see LEATHER). By first treating the hides with a melamine–formaldehyde resin, the leather is made more receptive to other tanning agents and the finished product has a lighter color. The amino resin is often referred to as a plumping agent because it makes the finished leather firmer and fuller.

Urea–formaldehyde resins are also used in the manufacture of foams. The resin solution containing an acid catalyst and a surface-active agent is foamed with air and cured. The open-cell type of foam absorbs water readily and is soft enough so that the stems of flowers can be easily processed into it. These features make the urea resin foam ideal for supporting floral displays. Urea–formaldehyde resin may also be foamed in place. A special nozzle brings the resin, catalyst, and foaming agent together. Air pressure is used to deposit the foam where it is desired, eg, within the outside walls of older houses to provide insulation. This application might be expected to grow as energy costs increase, if undesirable odors can be controlled.

Urea–formaldehyde resins are also used as the binder for the sand cores used in the molds for casting hollow metal shapes. The amino resin is mixed with moist sand and formed into the desired shape of the core. After drying and curing, the core is assembled into the mold and the molten metal poured in. Although the cured amino resin is strong enough to hold the core together while the hot metal is solidifying, it decomposes on longer heating. Later, the loose sand may be poured out of the hollow casting and recovered.

Regulatory Concerns

Both urea- and melamine–formaldehyde resins are of low toxicity. In the uncured state, the amino resin contains some free formaldehyde that could be objectionable. However, uncured resins have a very unpleasant taste that would discourage ingestion of more than trace amounts. The molded plastic, or the cured resin on textiles or paper may be considered nontoxic. Combustion or thermal decomposition of the cured resins can evolve toxic gases, such as formaldehyde, hydrogen cyanide, and oxides of nitrogen.

Melamine–formaldehyde resins may be used in paper which contacts aqueous and fatty foods according to 21 CFR 121.181.30. However, because a lower PEL has been established by OSHA, some mills are looking for alternatives. Approaches toward achieving lower formaldehyde levels in the resins have been reported (66,67); the efficacy of these systems needs to be established. Although alternative resins are available, significant changes in the papermaking operation would be required in order for them to be used effectively.

Economic Aspects

Japan produces more amino resin than any other country; the United States is next, with the Union of Soviet Socialist Republics, France, the United Kingdom, and Germany following.

Many large chemical companies produce amino resins and the raw materials needed, ie, formaldehyde, urea, and melamine. Some companies may buy raw materials to produce amino resins for use in their own products, such as plywood, chipboard, paper, textiles, or paints, and may also find it profitable to market these resins to smaller companies. The technology is highly developed and sales must be supported by adequate technical service to select the correct resin and see that it is applied under the best conditions.

Following is a list of major manufacturers of amino resins. Because of the highly specialized nature of amino resin technology many of these companies produce only a few types. Allied Chemical Corp., Specialty Chemicals Div., Morristown, N.J.; American Cyanamid Co., Industrial Chemicals and Plastics Div., Wayne, N.J.; Ashland Chemical Co., Div. Ashland Oil, Inc., Columbus, Ohio; BASF Canada Ltd., Station St. Laurent, Canada; Badische Aniline- und Soda-Fabrik A.G., Ludwigshafen, Germany; Berger Chemicals, Resinous Chemicals Div., Newcastle upon Tyne, England; Borden Chemical, Div. Borden, Inc., Columbus, Ohio; British Industrial Plastics, Ltd., Warley, West Midlands, England; British Oxygen Chemicals, Ltd., Chester-le-Street, Durham, England; Cassella Farbwerk Mainkur A.G., Frankfurt-Fechenheim, Germany; Celanese Resins, Div. Celanese Coatings Co., Louisville, Ky.; Commercial Solvents Corp., New York; Cook Paint and Varnish Co., Kansas City, Mo.; DSM, Utrecht, Holland; Dynamit Nobel, A.G., Troisdorf-Koln, Germany; Dynamit Nobel of America, Inc., Northvale, N.J.; Eronel Industries, Hawthorne, Calif.; Ferguson, James, & Sons, Ltd., London, England; Fiberite Corp., Winona, Minn.; Flexcraft Industries, Newark, N.J.; Ford Motor Co., Paint and Vinyl Operations, Mount Clemens, Mich.; George, P. D., Co., St. Louis, Mo.; Georgia-Pacific Corp., Chemical Div., Portland, Oreg.; Guardsman Chemical Coatings, Inc., Grand Rapids, Mich.; Gulf Oil Chemicals Co., Gulf Adhesives, Lansdale, Pa.; Hitachi Chemical Co., Ltd., Tokyo 160, Japan; Hoechst Aktiengesellschaft, D-6230 Frankfurt, Germany; Materiales Moldeables, S. A. de C. V., Mexico, D. F., Mexico; Matsushita Electric Works, Ltd., Kadoma-shi, Osaka-fu, Japan; Melamine Chemicals, Inc., Donaldsonville, La.; Monsanto Co., St. Louis, Mo.; Montedison SpA, Milano, Italy; Pacific Resins and Chemicals, Inc., Tacoma, Wash.; Patent Plastics Inc., Knoxville, Tenn.; Perstorp AB, Perstrop, Sweden; Plastics Engineering Co., Sheboygan, Wis.; Pierrefitte-Auby, Neuilly s Seine, France; Products Chimiques Ugine Kuhlmann, Div. Plastics, Paris, Fr.; Raymond Chemical Co., Toledo, Ohio; Reichhold Chemicals, Inc., White Plains, N.Y.; Rohm & Haas Co., Philadelphia, Pa.; Sullivan Chemical Coatings, Chicago, Ill.; and Sumitomo Bakelite Co., Ltd., Tokyo, Japan.

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AMMINES.

See COORDINATION COMPOUNDS.

AMMONIA

Ammonia [7664-41-7], NH₃, a colorless alkaline gas, is lighter than air and possesses a unique, penetrating odor. The preparation of ammonium salts dates back to the early Egyptians in the fourth century BC. Ammonia gas was first produced as a pure compound by Priestly in 1774.

The value of nitrogen compounds as an ingredient of mineral fertilizers was recognized in 1840. Nitrogen is an essential element to plant growth and ammonia is the primary nitrogen source used in fertilizers (qv). Until the early 1900s, the nitrogen source in farm soils was entirely derived from natural sources: from mineral resources such as Chilean nitrates, from manure and the putrefaction of vegetable wastes; and from ammonium sulfate from coal coking, seed meals, sewage sludges, and food processing by-products. The synthesis of ammonia directly from hydrogen [1333-74-0] (qv) and nitrogen [7727-37-9] (qv) on a commercial scale was pioneered by Haber and Bosch in 1913, for which they were awarded Nobel prizes. Further developments in economical, large scale ammonia production for fertilizers have made a significant impact on increases in the world's food supply.

Physical Properties

Table 1 lists the important physical properties of ammonia; Table 2 gives the densities at 15°C; Figure 1 is a Mollier diagram giving additional thermodynamic data for ammonia. The flammable limits of ammonia in air are 16 to 25% by volume; in oxygen the range is 15 to 79%. Such mixtures can explode although ammonia–air mixtures are quite difficult to ignite. The ignition temperature is about 650°C.

Table 1. Physical Properties of Anhydrous Ammonia

Property	Value
molecular weight	17.03
boiling point, °C	33.35
freezing point, °C	77.7
critical temp, °C	133.0
critical pressure, kPa ^a	11,425
specific heat, J (kg·K) ^b	
0°C	2097.2
100°C	2226.2
200°C	2105.6
heat of formation of gas, ΔH _f , kJ mol ^b	
0 K	39,222
298 K	46,222
solubility in water, wt %	
0°C	42.8
20°C	33.1
40°C	23.4
60°C	14.1
specific gravity	
40°C	0.690
0°C	0.639
40°C	0.580

^a To convert kPa to psi, multiply by 0.145.

^b To convert J to cal, divide by 4.184.

Table 2. Density of Aqueous Ammonia at 15°C

Ammonia, wt %	Density, g L
8	0.970
16	0.947
32	0.889
50	0.832
75	0.733
100	0.618

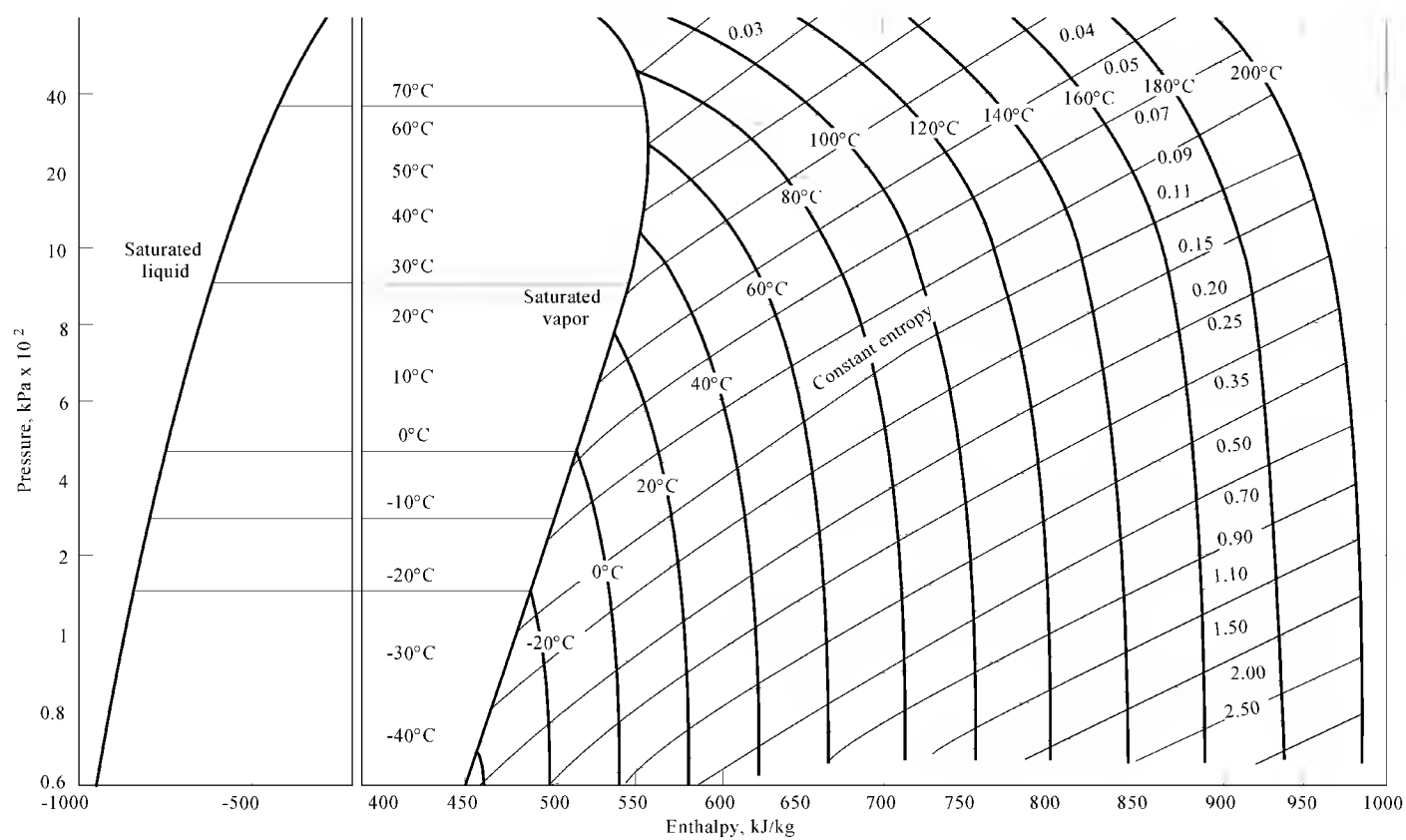


Fig. 1. Mollier diagram for ammonia. Numbers on dashed lines represent specific volume values in m³/kg. To convert from kPa to psi, multiply by 0.145. To convert kJ to kcal, divide by 4.184.

Courtesy of Elliot Company.

Ammonia is readily absorbed in water to make ammonia liquor. Figure 2 summarizes the vapor–liquid equilibria of aqueous ammonia solutions and Figure 3 shows the solution vapor pressures. Additional thermodynamic properties may be found in the literature (1,2). Considerable heat is evolved during the solution of ammonia in water: approximately 2180 kJ (520 kcal) of heat is evolved upon the dissolution of 1 kg of ammonia gas.

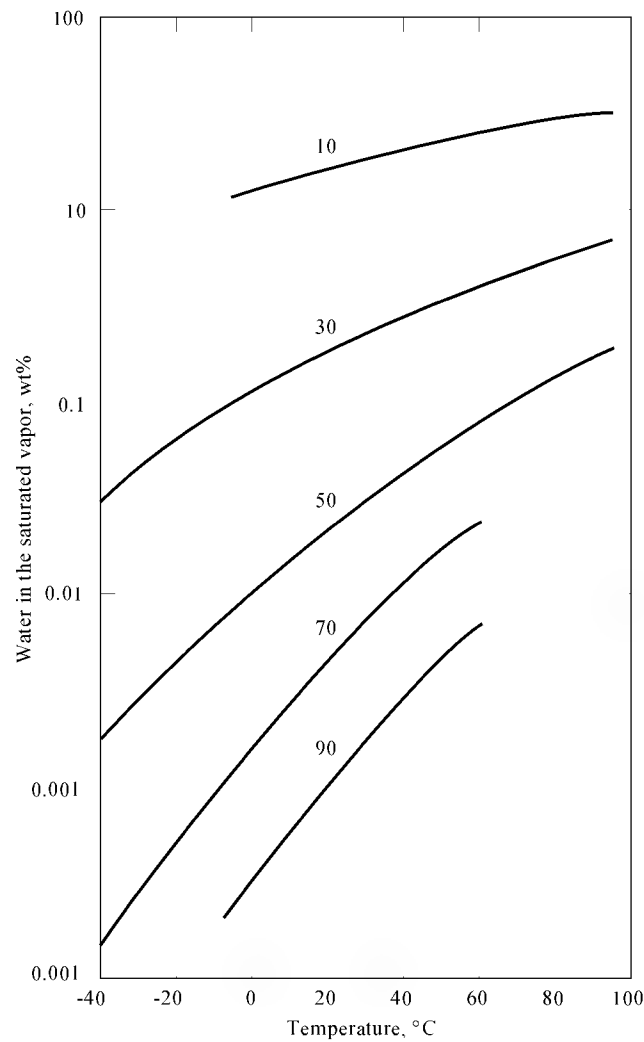


Fig. 2. Vapor–liquid equilibrium of ammonia–water system. Numbers represent the weight percent of ammonia in the liquid (1).

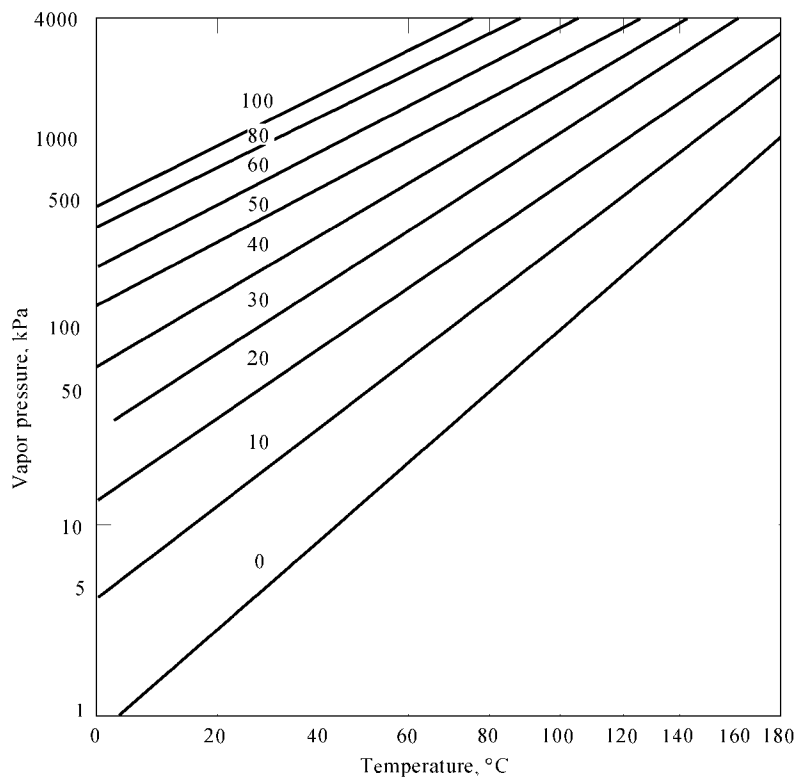


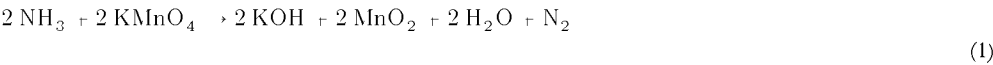
Fig. 3. Vapor pressure of aqueous ammonia solution (1). Numbers represent the weight percent of ammonia in the liquid. To convert kPa to psi, multiply by 0.145.

Ammonia is an excellent solvent for salts, and has an exceptional capacity to ionize electrolytes. The alkali metals and alkaline earth metals (except beryllium) are readily soluble in ammonia. Iodine, sulfur, and phosphorus dissolve in ammonia. In the presence of oxygen, copper is readily attacked by ammonia. Potassium, silver, and uranium are only slightly soluble. Both ammonium and beryllium chloride are very soluble, whereas most other metallic chlorides are slightly soluble or insoluble. Bromides are in general more soluble in ammonia than chlorides, and most of the iodides are more or less soluble. Oxides, fluorides, hydroxides, sulfates, sulfites, and carbonates are insoluble. Nitrates (eg, ammonium nitrate) and urea are soluble in both anhydrous and aqueous ammonia making the production of certain types of fertilizer nitrogen solutions possible. Many organic compounds such as amines (qv), nitro compounds, and aromatic sulfonic acids, also dissolve in liquid ammonia. Ammonia is superior to water in solvating organic compounds such as benzene (qv), carbon tetrachloride, and hexane.

Chemical Properties

Ammonia is comparatively stable at ordinary temperatures, but decomposes into hydrogen and nitrogen at elevated temperatures. The rate of decomposition is greatly affected by the nature of the surfaces with which the gas comes into contact: glass is very inactive; porcelain and pumice have a distinct accelerating effect; and metals such as iron, nickel, osmium, zinc, and uranium have even more of an effect. At atmospheric pressure, decomposition begins at about 450–500°C, whereas in the presence of catalysts, it begins as low as 300°C and is nearly complete at 500–600°C. At 1000°C, however, a trace of ammonia remains. Ammonia decomposition, a source of high purity hydrogen and nitrogen for use in metals processing, can also be promoted electrically or photochemically.

Ammonia reacts readily with a large variety of substances (see AMMONIUM COMPOUNDS; AMINES BY REDUCTION; AMINES). Oxidation at a high temperature is one of the more important reactions, giving nitrogen and water. Gaseous ammonia is oxidized to water and nitrogen when heated to a relatively high temperature in the presence of oxides of the less positive metals, such as cupric oxide. Powerful oxidizing agents, eg, potassium permanganate, react similarly at ordinary temperatures.



The action of chlorine on ammonia can also be regarded as an oxidation reaction.



A major step in the production of nitric acid [7697-37-2] (qv) is the catalytic oxidation of ammonia to nitric acid and water. Very short contact times on a platinum–rhodium catalyst at temperatures above 650°C are required.



The neutralization of acids is of commercial importance. Three principal fertilizers, ammonium nitrate [6484-52-2], NH₄NO₃, ammonium sulfate [7782-20-2], (NH₄)₂SO₄, and ammonium phosphate [10361-65-6], (NH₄)₃PO₄, are made by reaction of the respective acids with ammonia.

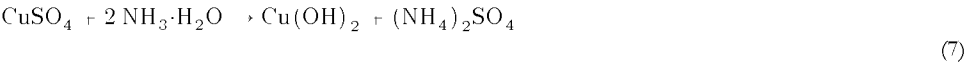
The reaction between ammonia and water is reversible.



The aqueous solubility of ammonia decreases rapidly as temperature increases. The existence of undissociated ammonium hydroxide [1336-21-6], NH₄OH,

in aqueous solution is doubtful although there are indications that ammonia exists in water in the form of the hydrates $\text{NH}_3\cdot\text{H}_2\text{O}$ and $2\text{NH}_3\cdot\text{H}_2\text{O}$. The ammonium ion, NH_4^+ , behaves similarly to the alkali metal cations. Ammonia, a comparatively weak base, however, ionizes in water to a much lesser extent than sodium hydroxide. In a molar solution of aqueous ammonia, the concentration of the hydroxyl ion is about two-hundredths that of the hydroxyl ion concentration in a molar sodium hydroxide solution.

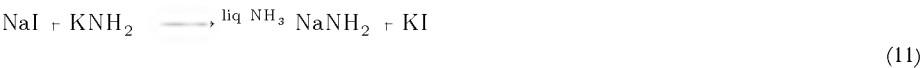
Aqueous ammonia also acts as a base precipitating metallic hydroxides from solutions of their salts, and in forming complex ions in the presence of excess ammonia. For example, using copper sulfate solution, cupric hydroxide, which is at first precipitated, redissolves in excess ammonia because of the formation of the complex tetramminecopper(II) ion.



Potassium dissolves in liquid ammonia, but the conversion of a small amount of the metallic potassium to the metallic amide takes several days. By applying the same technique using sodium metal, sodium amide [7782-92-5], NaNH_2 , a white solid, can be formed.



Heating metallic lithium in a stream of gaseous ammonia gives lithium amide [7782-89-0] LiNH_2 , which may also be prepared from liquid ammonia and lithium in the presence of platinum black. Amides of the alkali metals can be prepared by double-decomposition reactions in liquid ammonia. For example



Heating ammonia with a reactive metal, such as magnesium, gives the nitride.



Magnesium reacts slowly at lower temperatures to give the amide, as do all active metals; this reaction is catalyzed by transition metal ions. Aluminum nitride [24304-00-5], AlN , barium nitride [12047-79-9], Ba_3N_2 , calcium nitride [12013-82-0], Ca_3N_2 , strontium nitride [12033-82-8], Sr_3N_2 , and titanium nitride [25583-20-4], TiN , may be formed by heating the corresponding amides.

Halogens react with ammonia. Chlorine or bromine liberate nitrogen from excess ammonia and give the corresponding ammonium salt. Substitution probably takes place first. The resulting trihalide combines loosely with another molecule of ammonia, to give $\text{NCl}_3\cdot\text{NH}_3$ for example. These ammoniates are very unstable and decompose in the presence of excess ammonia to give the ammonium salt and nitrogen.



The iodine compound is more stable and separates as so-called nitrogen triiodide monoammoniate [14014-86-9], $\text{NI}_3\cdot\text{NH}_3$, an insoluble brownish-black solid, which decomposes when exposed to light in the presence of ammonia. In reactions of the halogens with the respective ammonium salts, however, the action is different. Chlorine replaces hydrogen and nitrogen chloride [10025-85-1], NCl_3 , separates as oily, yellow droplets capable of spontaneous explosive decomposition.



The hydrogen of the ammonium salt is not replaced by bromine and iodine. These elements combine with the salt to form perhalides.



A number of perhalides are known, and one of the most stable is ammonium tetrachloroiodide [19702-43-3], NH_4ICl_4 . Ammonia reacts with chlorine in dilute solution to give chloramines, a reaction important in water purification (see CHLORAMINES AND BROMAMINES). Depending upon the pH of the water, either monochloramine [10599-90-3], NH_2Cl , or dichloramine [3400-09-7], NHCl_2 , is formed. In the dilutions encountered in waterworks practice, monochloramine is nearly always found, except in the case of very acidic water (see BLEACHING AGENTS; WATER).

Ammonia reacts with phosphorus vapor at red heat to give nitrogen and phosphine.



Sulfur vapor and ammonia react to give ammonium sulfide and nitrogen; sulfur and liquid anhydrous ammonia react to produce nitrogen sulfide [28950-34-7], N_4S_4 .



Ammonia and carbon at red heat give ammonium cyanide [12211-52-8], NH_4CN .

Ammonia forms a great variety of addition or coordination compounds (qv), also called ammoniates, in analogy with hydrates. Thus $\text{CaCl}_2\cdot 6\text{NH}_3$ and $\text{CuSO}_4\cdot 4\text{NH}_3$ are comparable to $\text{CaCl}_2\cdot 6\text{H}_2\text{O}$ and $\text{CuSO}_4\cdot 4\text{H}_2\text{O}$, respectively, and, when regarded as coordination compounds, are called amines and written as complexes, eg, $[\text{Cu}(\text{NH}_3)_4]\text{SO}_4$. The solubility in water of such compounds is often quite different from the solubility of the parent salts. For example, silver chloride, AgCl , is almost insoluble in water, whereas $[\text{Ag}(\text{NH}_3)_2]\text{Cl}$ is readily soluble. Thus silver chloride dissolves in aqueous ammonia. Similar reactions take place with other water insoluble silver and copper salts. Many amines can be obtained in a crystalline form, particularly those of cobalt, chromium, and platinum.

Of major industrial importance is the reaction of ammonia and carbon dioxide giving ammonium carbamate [1111-78-0], $\text{CH}_3\text{N}_2\text{O}_2$.



which then decomposes to urea (qv) and water



This is an example of an ammonolytic reaction in which a chemical bond is broken by the addition of ammonia. It is analogous to the hydrolysis reactions of water. An impressive number of inorganic and organic compounds undergo ammonolysis.

Manufacture

Ammonium compounds were produced in the 1890s on a large scale as by-product ammonium sulfate [7783-20-2] from coke oven gas. Coke oven gas also provided the feedstock for the Haber-Bosch process, the first technology to synthesize ammonia directly from elemental hydrogen and nitrogen. The first commercial Haber-Bosch installation went on stream in 1913 at a Badische Anilin and Soda Fabrik (BASF) facility in Ludwigshafen-Oppau, Germany. It had a design capacity of 30 metric tons per day. The successful commercialization of this process not only produced first-of-a-kind high temperature and pressure equipment designs but also resulted in the promoted iron catalyst which is essentially still used for ammonia synthesis.

Between 1930 and 1950, the primary emphasis of ammonia process development was in the area of synthesis gas generation (3) (see FUELS, SYNTHETIC, GASEOUS FUELS). Extensive coal deposits in Europe provided the feedstock for the ammonia industry. The North American ammonia industry was based primarily on abundant supplies of low cost natural gas (see GAS, NATURAL).

Natural gas reforming at successively higher pressures resulted in lower downstream compression requirements. By the early 1960s, the expensive and cumbersome copper liquor process for final carbon oxide removal was being replaced by methanation, which permitted two-stage shift conversion with resultant low carbon monoxide leakage. The development of the second stage low temperature shift catalyst further improved the efficiency of the process by increasing the ultimate hydrogen yield from synthesis gas.

A step change in the capacity attainable from single-train plants occurred in 1963 with the commissioning of a 544 t d unit designed by The M. W. Kellogg Company; this was followed by a similar size plant for Monsanto in Luling, Louisiana. The Monsanto plant marked the first time centrifugal compressors were used for all process services using full integration with utility systems. These innovations were the forerunner for the large scale single-train 907 and 1500 t d plant designs which proliferated in the 1970s.

Rapid expansion resulted from engineering efforts to meet an increasing world demand for fixed nitrogen. Improvements in the energy cycle, including high pressure steam generation from waste heat, and technical advances in compressors, reformers, and converters (4,5) all led to more efficient ammonia production taking full advantage of the economy of scale provided by large tonnage single-train plants.

Thermodynamics and Kinetics. Ammonia is synthesized by the reversible reaction of hydrogen and nitrogen.



Essential for synthesis considerations is the ability to determine the amount of ammonia present in an equilibrium mixture at various temperatures and pressures. Reliable data on equilibrium mixtures for pressures ranging from 1,000 to 101,000 kPa (10–1000 atm) were developed early on (6–8) and resulted in the determination of the reaction equilibrium constant (9). Experimental data indicates that K_p is dependent not only on temperature and pressure, but also upon the ratio of hydrogen and nitrogen present. Table 3 lists values for the ammonia equilibrium concentration calculated for a feed using a 3:1 hydrogen to nitrogen ratio and either 0 or 10% inerts (10).

Table 3. Equilibrium Percent of Ammonia for a Gas Containing a Hydrogen to Nitrogen Ratio of 3:1 at Various Pressures^a

Temperature, K	Equilibrium % at pressure, kPa ^b			
	10,133	20,265	30,398	40,530
Using 0% inerts				
633	35.10	49.62	58.91	65.72
673	25.37	38.82	48.18	55.39
713	17.92	29.46	38.18	45.26
753	12.55	21.91	29.52	36.03
793	8.32	16.13	22.48	28.14
833	6.27	11.88	16.99	21.73
873	4.53	8.80	12.84	16.72
Using 10% inerts ^c				
633	28.63	40.53	48.14	53.70
673	20.68	31.71	39.38	45.29
713	14.60	24.06	31.21	37.02
753	10.22	17.88	24.14	29.48
793	7.18	13.16	18.38	23.04
833	5.10	9.68	13.88	17.79
873	3.69	7.17	10.49	13.68

^a Ref. 10.
^b To convert kPa to atm, divide by 101.3.
^c 3% argon and 7% methane are present.

In the design of synthesis facilities, the rate at which the ammonia is formed has to be considered. The most widely used equation for the intrinsic rate of reaction is the Temkin-Pyzher equation (11):

$$\omega = K_1 P_{\text{N}_2} \left(\frac{P_{\text{H}_2}^3}{P_{\text{NH}_3}^2} \right)^\gamma - K_2 \left(\frac{P_{\text{NH}_3}^2}{P_{\text{H}_2}^3} \right)^{(1-\gamma)}$$

(21)

where ω is the conversion rate, ie, the difference between the synthesis and decomposition rates; K_1 and K_2 , are rate constants for synthesis and decomposition, respectively; P , partial pressure of the species indicated; and γ , is constant (reaction order), 0.75 (12) and 0.5–0.7 (13–15). The Temkin-Pyzhev equation assumes that the chemisorption of nitrogen on a nonuniform surface is rate-controlling and no diffusion limitations are considered. A modified Temkin-Pyzhev is normally applied to commercial reactor design to account for diffusion limitations and the presence of poisons (16–19). The following equation for the heat of reaction as a function of temperature T and pressure p has been proposed (20).

$$\begin{aligned} \Delta H = & [2.2523 \times 10^{-2} + 34.7236 T + 1.89905 \times 10^7 T^3] p \\ & - 22.3792 T - 1.057 \times 10^{-3} T^2 + 7.08048 \times 10^{-6} T^3 \\ & 38327.0 \end{aligned}$$

(22)

The heat of reaction ΔH is given in joules per gram mole of ammonia formed. Equation 22 ignores the heat of mixing which must be taken into account for application to industrial situations (21,22). The heat evolved in synthesis at 370–540°C is approximately 54,430 kJ mol (23, 400 Btu lb-mol).

The industrial-scale reaction of hydrogen and nitrogen to form ammonia is always carried out on a catalytic surface. Most commercial catalysts are based on metallic iron, produced mostly from magnetite, Fe_3O_4 , that has been promoted using alkali in the form of potash and metals, such as aluminum, calcium, or magnesium. The catalyst is susceptible to thermal degradation and various poisons. Oxygen bearing compounds have a temporary poisoning effect that is reversible if the exposure is only for short periods. Sulfur, arsenic, phosphorus, chlorine, and heavy hydrocarbons cause permanent poisoning.

Recent commercialization efforts have focused on improved activity synthesis catalysts, which allow ammonia synthesis to be conducted at significantly lower pressures and temperatures. Catalyst manufacturers have focused on enhancing the activity of the iron-based catalyst through the use of promoters (23).

A fundamentally different ammonia synthesis catalyst of promoted ruthenium on a high surface area graphite support has been developed (24). The catalyst system is said to offer greatly improved activity at high ammonia concentrations for a wide range of hydrogen to nitrogen ratios coupled with excellent low pressure and low temperature performance (25). Kellogg's Advanced Ammonia Process (KAAP) incorporates the unique properties of this catalyst in a highly efficient ammonia plant design (26).

Several variables affect ammonia synthesis.

Synthesis Pressure. The ammonia reaction proceeds with a decrease in volume; therefore, according to Le Chatelier's principle, an increase in pressure increases the equilibrium percentage of ammonia. The reaction rate is also accelerated by increasing the pressure.

Synthesis Temperature. Because of the exothermic nature of the ammonia synthesis reaction, higher temperatures increase reaction rates, but the equilibrium amount of ammonia decreases. Thermal degradation of the catalyst also increases with temperature.

Space Velocity. The space velocity is the ratio of the volumetric rate of gas at standard conditions to the volume of the catalyst. Generally, the percentage of ammonia in the existing gas decreases as space velocity increases; however, the same volume of catalyst at the increased space velocities is capable of producing more ammonia (Fig. 4) (27). Normally space velocities for commercial operations are between 8,000 and 60,000 h^{-1} .

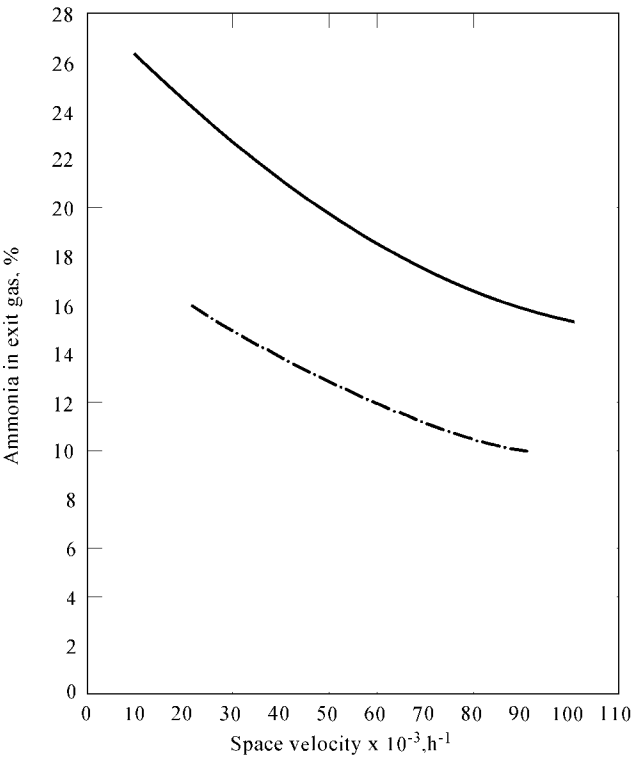


Fig. 4. Ammonia in exit gas as a function of space velocity (10) at (—) 32, 120 and (---) 15, 300 kPa. To convert kPa to psi, multiply by 0.145.

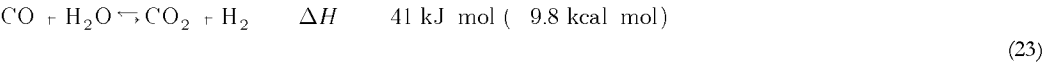
Inlet Gas Composition. The effect of inlet gas composition varies depending on the inerts level (see Table 3), ammonia concentration, and hydrogen-to-nitrogen ratio. Ammonia in the incoming gas affects the reaction rate. Most commercial facilities operate at a hydrogen-to-nitrogen ratio of 3:1; however, the optimum may be something less than that (28). Some plants have been designed to operate at a hydrogen to nitrogen ratio in the range of 2.0 to 2.8 (25,29,30).

Catalyst Particle Size. Catalyst activity increases as catalyst particles decrease in size and the ratio of the catalyst's surface area to its volume increases. Small catalyst particles also have a lower resistance to mass transfer within the catalyst pore structure. Catalysts are available in a wide range of sizes. Axial flow converters predominantly use those in the 6–10 mm range whereas the radial and horizontal designs take advantage of the increased activity of the 1.5–3.0 mm size.

Synthesis Gas Preparation Processes. Synthesis gas for ammonia production consists of hydrogen and nitrogen in about a three to one mole ratio, residual methane, argon introduced with the process air, and traces of carbon oxides. There are several processes available for synthesis gas generation and each is characterized by the specific feedstock used. A typical synthesis gas composition by volume is: hydrogen, 73.65%; nitrogen, 24.55%; methane, <1 ppm–0.8%; argon, 100 ppm–0.34%; carbon oxides, 2–10 ppm; and water vapor, 0.1 ppm.

The source of nitrogen is always air. However, hydrogen can be derived from a variety of raw materials including water, light and heavy hydrocarbons (qv) resulting from crude oil refining, coal (qv), natural gas, and sometimes a combination of these raw materials. In all cases, part of the hydrogen produced is derived from water.

Synthesis gas preparation consists of three steps: (1) feedstock conversion, (2) carbon monoxide conversion, and (3) gas purification. Table 4 gives the main processes for each of the feedstocks (qv) used. In each case, except for water electrolysis, concomitant to the reactions shown, the water-gas shift reaction occurs.



Equilibrium is achieved in steam reforming; equilibrium is approached for partial oxidation process.

Table 4. Hydrogen Generation Raw Materials and Processes

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Raw material	Process description	Feedstock conversion reaction
natural gas	steam reforming ^a	$C_nH_{2n+2} + nH_2O \rightleftharpoons nCO + (2n+1)H_2$
naphtha	steam reforming ^b	$C_nH_{2n+2} + nH_2O \rightleftharpoons nCO + (2n+1)H_2$
fuel oil	partial oxidation	$C_nH_{2n+2} + n2O_2 \rightleftharpoons nCO + (n+1)H_2$
coal	coal gasification	$C + 12O_2 \rightleftharpoons CO$
water	electrolysis	$H_2O \xrightarrow{e^-} 12O_2 + H_2$

^a Nickel is used as catalyst.
^b Promoted nickel is used as catalyst.

In the original Haber-Bosch process, the hydrogen source was coke derived from coal. In this process, shown in Figure 5, coke is first blasted with air and the heat liberated by the formation of carbon dioxide raises the coke to incandescence. The products of combustion leave the system by going to the atmosphere. Steam is added next to produce water gas containing carbon dioxide, carbon monoxide, and hydrogen. The nitrogen is usually furnished by adding a sufficient quantity of the combustion products from the blasting step to the gas stream. Dust particles and undecomposed steam are then removed by water scrubbing. A gas holder provides storage. The carbon monoxide in the gas is converted to hydrogen and carbon dioxide by reaction with steam over a catalyst and the converted gas is stored in another gas holder, compressed, and the carbon dioxide removed by water scrubbing. The gas is then compressed and scrubbed using an ammoniacal cuprous solution to remove unconverted carbon monoxide. The resultant, relatively pure gas, consisting of three parts hydrogen to one part nitrogen, is then fed as makeup gas to the synthesis loop.

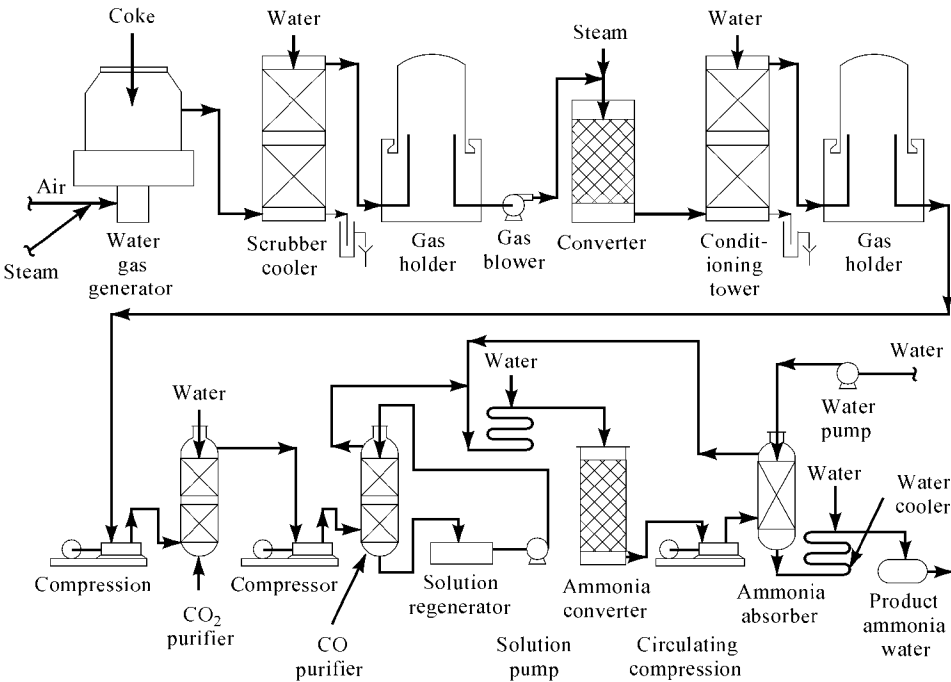


Fig. 5. Haber-Bosch process flow diagram.

The most economic hydrocarbon feedstock is likely to be the one having the highest hydrogen to carbon ratio. From Table 4 it can be seen that, for a given amount of carbon (feed), proportionally more hydrogen is generated by steam reforming than by partial oxidation. Thus, in the manufacture of hydrogen for ammonia synthesis, partial oxidation processes require more feed, ultimately leading to larger carbon dioxide removal facilities. In addition, the raw synthesis gas generated by partial oxidation is much higher in carbon monoxide content than that coming from a steam reforming operation. This high CO content requires larger facilities, both in terms of equipment and catalyst, for shift conversion. Because more CO₂ removal and higher shift conversion lead to higher investment and operating costs, partial oxidation processes are normally used only for materials which cannot be handled by steam reforming such as coal or heavy hydrocarbon feeds.

Hydrogen produced by the electrolysis of water is used in special circumstances only: where electric power is plentiful, inexpensive, and light hydrocarbons are not available.

Catalytic reformer off-gases from oil refinery gasoline production have been a source of hydrogen. Several ammonia plants have been built using this off-gas which is usually about 85% hydrogen, as raw material feed. In such installations, a liquid nitrogen wash system is used to remove the undesirable impurities in the gas feed and to provide the nitrogen required for synthesis. Because of increased demand for hydrogen in refinery hydro-treating operations, little by-product hydrogen is available and generally additional hydrogen is needed. Therefore, fewer ammonia plants using reformer off-gas have been built than in the past.

Of the raw material hydrogen sources—natural gas, coal, and petroleum fractions—natural gas is the most often employed in ammonia plants in the 1990s and steam reforming is by far the most often used process. Partial oxidation processes are utilized where steam-reformable feeds are not available or in special situations where local conditions exist to provide favorable economics. Table 5 lists the contribution of the various feedstocks to world ammonia capacity in 1983 and 1987 (31).

Table 5. Feedstocks for World Ammonia Capacity, Annual %

Feedstock	1983	1987
natural gas	66.4	69.8
natural gas hybrid ^a	7.5	5.8
naphtha, fuel oil, condensate	12.4	10.5
coke oven, refinery gas, hydrogen	4.3	3.9
coal	10.8	10.0
Total	100.0	100.0

^a Hybrid plants are naphtha and fuel oil-based plants modified to use natural gas.

Coal-Based Partial Oxidation Processes Two commercially established processes utilizing coal feeds are the Lurgi process (32) and the Koppers-Totzek process (33); the process schemes are shown in Figures 6 and 7, respectively.

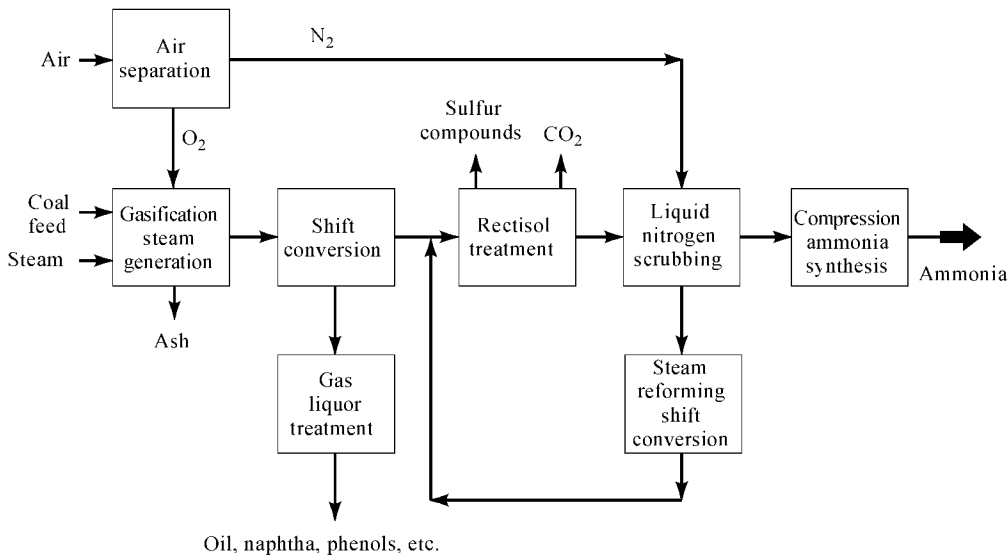


Fig. 6. Flow sheet for ammonia production from Lurgi coal gasification.

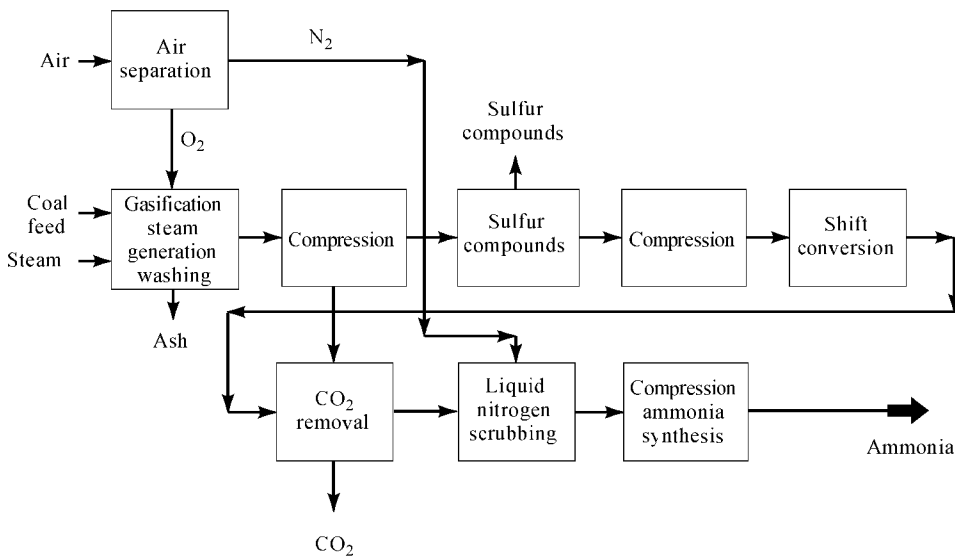


Fig. 7. Flow sheet for ammonia production from Koppers-Totzek coal gasification.

In the Lurgi process, coal is gasified in a fixed bed reactor using oxygen and steam at about 2000–3000 kPa (20–30 atm). The steam and oxygen enter the gasifier through slots in a rotary grate while the coal is charged through specially designed lock hoppers and distributed evenly over the cross section of the gasifier. Ash is removed in a nonslagging operation by the rotary grate. Gasification temperatures range from about 560°C to 620°C depending on the feed characteristics. Because the gasification temperature is in the intermediate range and the operating pressure is relatively high, the methane and carbon dioxide content in the crude gas is considerably greater than for conventional reforming and partial oxidation processes. The methane and carbon dioxide contents from a typical Lurgi gasifier are 10–11% and about 28%, respectively. The crude gas from the Lurgi gasifier is treated in several processing steps including waste heat recovery, shift conversion, removal of tars, phenols, and other by-products, Rectisol (methanol wash) treatment for carbon dioxide and sulfur removal, liquid nitrogen scrubbing to produce a highly purified synthesis gas, compression, and finally ammonia synthesis. The liquid nitrogen scrubbing step removes carbon monoxide and methane which are recycled to a side stream steam reforming and shift facility for production of additional hydrogen and serves to introduce the nitrogen required for synthesis.

The Koppers-Totzek dilute phase gasification takes place at low pressures and much higher temperatures essentially ensuring complete hydrocarbon conversion. A homogeneous mixture of pulverized coal, oxygen, and steam reacts producing a flame zone temperature of about 1925°C. Subsequent steam and carbon endothermic reactions reduce the temperature to around 1480°C. Residual methane levels of 0.1% and less are realized. Depending on the reactivity of the coal, up to 99% of the carbon is gasified; the bulk of the resultant gas consists of hydrogen and carbon monoxide. The crude gas is processed in a series of operations consisting of steam generation, washing, compression, sulfur removal, shift conversion, carbon dioxide removal, nitrogen scrubbing, compression, and synthesis.

Worldwide interest in synfuels in the mid-1970s produced a variety of developing coal utilization technologies, ranging from direct liquefaction to *in situ* gasification (34,35) (see COAL CONVERSION PROCESSES). Processes best suited for ammonia production would operate at high pressures and coal conversions, having low methane slip and by-product formation. However, even with improved technologies, ammonia from coal plants is more costly than from conventional gas- or liquid-based processes because of the extensive solids handling and effluent treatment facilities required.

Increasing development of abundant oil and gas reserves has precluded significant exploitation of coal as a chemical feedstock. The Texaco coal gasification technology was demonstrated on a small industrial scale in 1982 at a Tennessee Valley Authority (TVA) facility in Alabama (36). A single Texaco coal gasifier was retrofitted to the front-end of an existing natural gas-based ammonia plant to provide synthesis gas for equivalent production of 122 t/d. In 1984 Ube Industries in Japan commissioned a new front-end based on this technology, which fed an existing Kellogg 1500 t/d ammonia synthesis loop (37). This Ube facility is now flexible enough to produce ammonia from coal, petroleum coke, naphtha, or LPG as required.

Heavy Hydrocarbon-Based Partial Oxidation Processes. Two major partial oxidation processes are commercially available, the Shell process (38) and the Texaco process (39). Operating conditions in the gas generator vary from 1200°C to 1370°C and from 3100 kPa to 8270 kPa (450–1200 psig). Generally, heavy oils are the hydrocarbon feeds; however, the process can also accommodate feeds from natural gas to residual oils.

Figure 8 shows a schematic of the Shell Gasification process. Preheated hydrocarbon feed and oxygen are mixed with steam and fed to the

combustion chamber of the reactor. A noncatalytic flame reaction produces the raw synthesis gas. The hot reactor effluent is cooled by generating high pressure steam in specially designed waste heat boilers. In spite of the presence of free carbon in the gas, the design ensures that heat transfer surfaces remain clean even after prolonged operation. The raw synthesis gas is then routed to the carbon removal system, consisting of a carbon catcher and gas cooler scrubber, where the carbon produced in the reactor is removed as a water slurry. The carbon is transferred to the oil to form carbon–oil pellets in a device called a pelletizer. The resultant pellets are reslurried with oil feed in a homogenizer and recycled as a dilute slurry to the reactor.

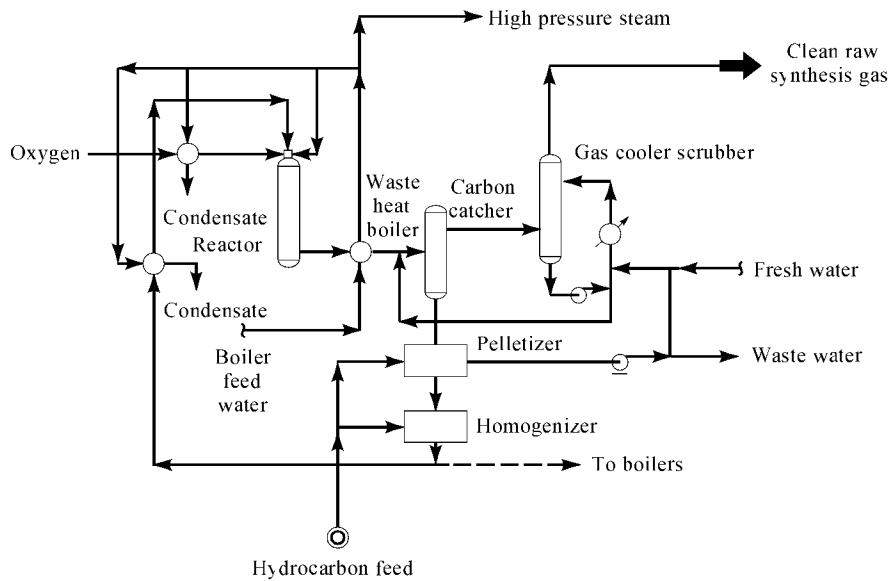


Fig. 8. Shell gasification process.

Figure 9 shows a schematic of the Texaco gasification process. Preheated hydrocarbon feed along with oxygen and steam are fed to the reactor. The hot raw synthesis gas is quenched in the lower portion of the reactor using a hot water stream from the scrubber. The water quench cools the gas to saturation temperature by way of vaporization and allows for the subsequent shift conversion. Most of the remaining carbon is removed in the quench operation and further cleanup is accomplished in the scrubber. Carbon in the water stream leaving the reactor is extracted with naphtha in the naphtha separator. The lighter naphtha–carbon layer is mixed with incoming hydrocarbon feed and the resultant mixture is regenerated in the naphtha stripper. From the stripper overheads, naphtha is recycled back to the carbon extraction step. The bottoms from the naphtha stripper containing carbon is recycled to the reactor. The water from the naphtha separator, after degassing, is routed back to the scrubber and the clean raw synthesis gas is available for further processing.

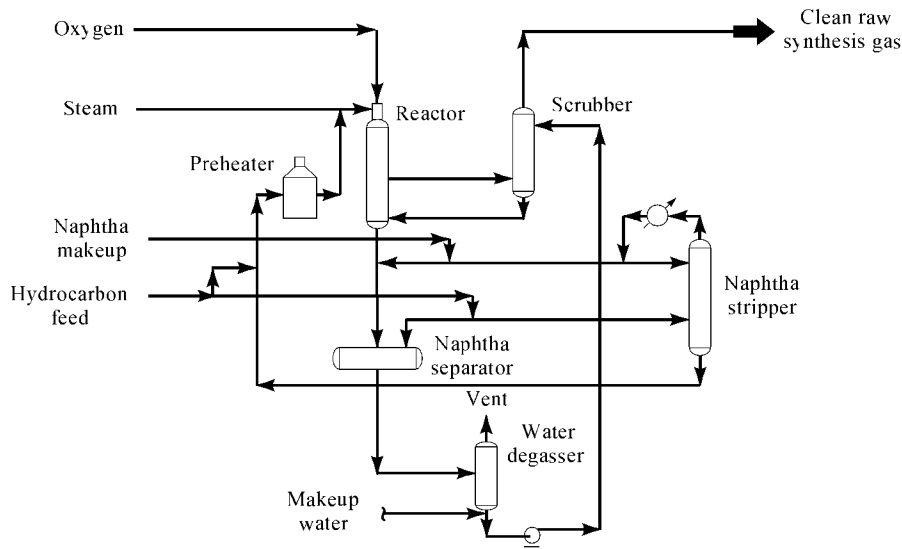


Fig. 9. Texaco gasification process.

Ammonia production by partial oxidation of hydrocarbon feeds depends to some degree on the gasification step. The clean raw synthesis gas from a Shell partial oxidation system is first treated for sulfur removal, then passed through shift conversion. A liquid nitrogen scrubbing step follows. The saturated, cleaned raw synthesis gas from a Texaco partial oxidation system is first shifted by use of a sulfur resistant catalyst. Steam required for shifting is already present in the gas by way of the quench operation in the generator. The shifted gas is then processed for hydrogen sulfide and carbon dioxide removal followed by liquid nitrogen scrubbing.

Steam Reforming. The bulk, roughly 75–80%, of world ammonia production is realized from steam reforming operations and approximately 65–70% of these use natural gas feed. Figure 10 is a flow sheet for a typical process based on light hydrocarbon feeds. The feedstock, ranging from natural gas to naphtha, is first desulfurized, then mixed with steam and reformed in the primary reformer. Sufficient air, containing the required amount of nitrogen for synthesis, is introduced in the secondary reforming step. The reformed gas is then shifted and scrubbed for CO₂ removal. The remaining carbon dioxide and carbon monoxide are removed by reaction of hydrogen to produce methane and water in a methanation step. The synthesis gas is then compressed and ammonia is produced.

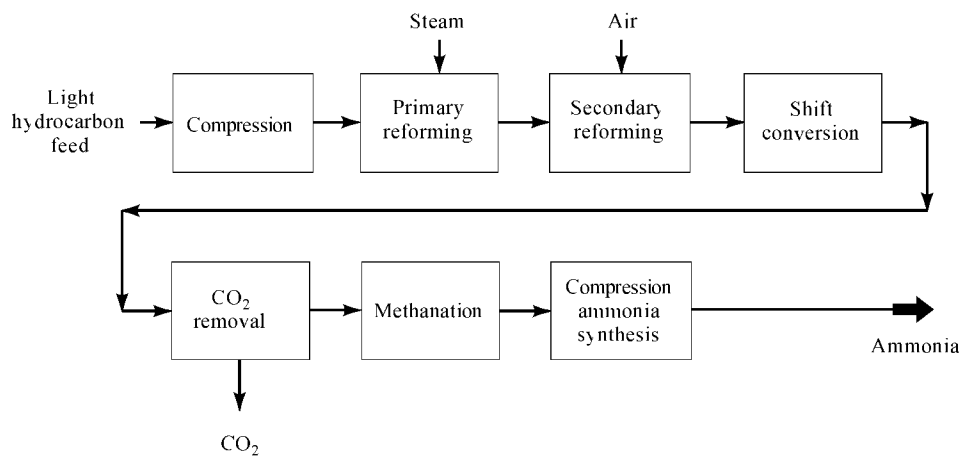


Fig. 10. Flow sheet for ammonia processing from steam reforming.

Capital Cost and Energy. The capital cost and energy requirements for ammonia production are largely dependent on the feedstocks employed. Table 6 presents the energy requirements for a large scale ammonia plant using various feedstocks (36). Energy usage increases significantly as the feedstock changes from natural gas to coal or water. A retrofitted coal gasification ammonia plant has an energy consumption of 44.3 GJ t (37). New coal gasification technologies such as the Kellogg KRW process can reduce the energy consumption by about 10% compared to other processes (40).

Table 6. Energy Required for Ammonia Production based on Feedstock Process, GJ/t

	Natural gas reforming	Naphtha reforming	Fuel oil partial-ox	Coal gasification	Water electrolysis
1970s plant	35.9	39.6	40.6	48.5	44.3
1980s plant	29.0	32.0		43.2	

Capital costs which follow the same trend as energy consumption, can be about 1.5 to 2.0 times for partial oxidation and coal gasification, respectively, that for natural gas reforming (41). A naphtha reforming plant would cost about 15–20% more than one based on natural gas because of the requirement for hydrotreating facilities and a larger front-end needed for carbon dioxide removal.

Hydrogen-Rich Off-Gases For Synthesis Gas. Since the mid- 1970s there has been more emphasis placed on using by-product hydrogen or off-gases rich in hydrogen for ammonia production. Table 7 lists processes which produce H₂-rich off-gases (42). These systems usually contain other impurities which must be removed before ammonia synthesis.

Table 7. Sources and Composition of H₂-Rich Gases

H ₂ -rich gas stream	Composition, vol %				
	H ₂	CO	CO ₂	CH ₄	N ₂
methanol purge gas ^a	80.0	2.00	2.60	14.0	1.0
ethylene plant H ₂ gas ^b	84.4	0.20		15.4	
CO plant H ₂ gas ^c	97.0	1.95		0.4	0.09
caustic soda plant H ₂ ^d	99.86		0.02		0.24
cyclar and BTX plants	96.6			4.0	
coke oven gas ^e	60.0	6.5	2.5	22.5	6.5

^a Gas also contains 0.4 vol % methanol.

^b Based on ethane feed.

^c CO plant based on cold box for CO conversion.

^d Gas also contains 0.06 vol % oxygen and 15 ppm chlorine.

^e Gas also contains about 1.5 vol % hydrocarbons after pretreatment and 0.5 vol % oxygen.

A typical ammonia production facility using methanol plant purge gas as feedstock is shown schematically in Figure 11. This is a nominal 545 t d ammonia plant commissioned in 1986 for Ocelot, in Kitimat, B.C., Canada. It uses Kellogg's reduced energy synthesis loop with a horizontal intercooled ammonia converter and a unitized chiller–flash drum system, a first-of-kind equipment installation. A similar 750 t d plant was constructed in 1989 in the United Kingdom, utilizing by-product hydrogen from carbon monoxide plants.

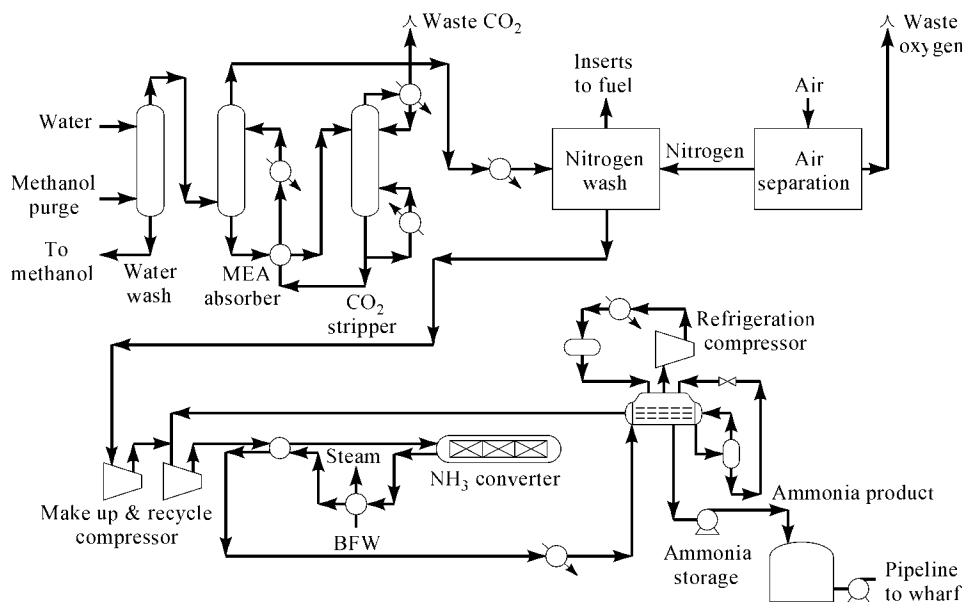


Fig. 11. Ocelot plant flow diagram. MEA, monoethanolamine; BFW, boiler feed water.

Future Sources of Synthesis Gas. The energy intensive nature of ammonia production and the worldwide energy crisis in the 1970s led to the proposal of new concepts for synthesis gas generation that do not require hydrocarbon feedstock. For example, the use of waste heat from nuclear installations has been proposed for replacing the fuel required for synthesis gas generation as has the use of thermal energy from the ocean (see THERMAL POLLUTION). An installation called Ocean Thermal Energy Conversion (OTEC) Ammonia Plant-Ship has been proposed (43). In this scheme, a working fluid (ammonia) is pumped from the deeper (colder) part of the ocean to the surface (warmer), where it evaporates and the ammonia vapor so generated is expanded to provide shaft power to an electric generator. After expansion, the ammonia vapor is condensed and the energy cycle is completed. The power generated is used for water electrolysis to produce H_2 ; water for the electrolytic cells comes from reverse osmosis. The hydrogen is combined with nitrogen from an air liquefaction plant and the H_2-N_2 mixture is sent to a conventional ammonia synthesis loop. The entire plant is supported by the electricity produced by the thermal gradient in the ocean. Energy contained in ocean tidal waves, shallow but large masses of water built up by electric power plants during off-peak hours, in wind, etc have all been considered as alternatives to fossil fuel-based energy.

In the 1980s, however, the prices of oil and natural gas reversed their upward trends. Natural gas discoveries, both on-shore and off-shore, have considerably increased the world's energy supply and oil discoveries, many with associated gas, contributed more feedstock potential for ammonia production.

Based on these developments, the foreseeable future sources of ammonia synthesis gas are expected to be mainly from steam reforming of natural gas, supplemented by associated gas from oil production, and hydrogen rich off-gases (especially from methanol plants).

Steam-Reforming Natural Gas. Natural gas is the single most common raw material for the manufacture of ammonia. A typical flow sheet for a high capacity single-train ammonia plant is indicated in Figure 12. The important process steps are: feedstock purification, primary and secondary reforming, shift conversion, carbon dioxide removal, synthesis gas purification, ammonia synthesis, and recovery.

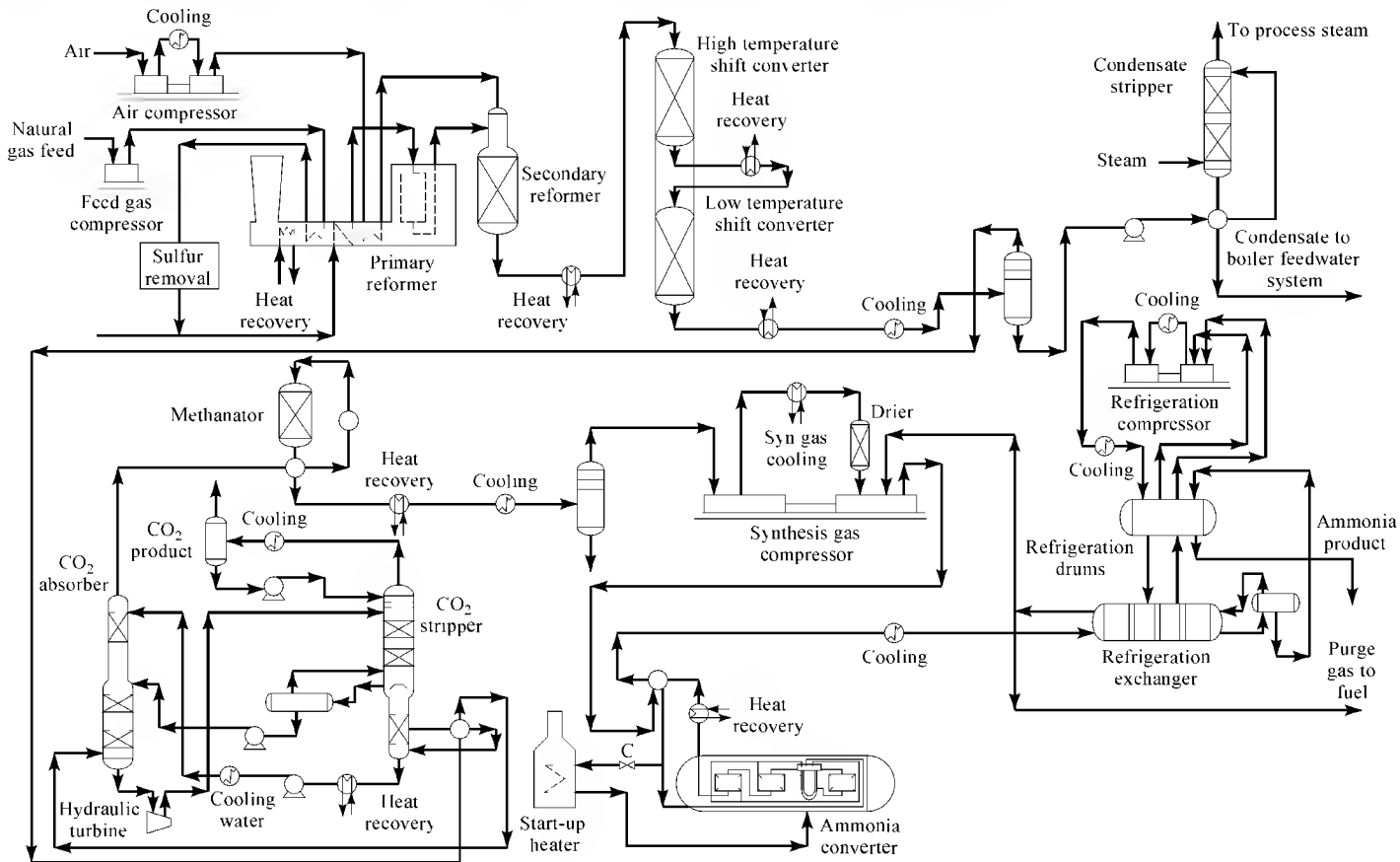


Fig. 12. Flow sheet for a Kellogg high capacity single-train ammonia plant.

Feed Gas Purification. Because nickel-based reforming catalysts are quite sensitive to sulfur, halogen, and heavy metal poisons which may be found in natural gas, a feedstock purification system is normally required. Sulfur compounds, in both organic and inorganic forms, are the most common

reforming catalyst poisons found in natural gas. Activated carbon and hot or cold zinc oxide beds are generally used to remove sulfur compounds (see CARBON, ACTIVATED CARBON). Low levels of sulfur can be adsorbed on activated carbon at ambient temperatures (see ADSORPTION, GAS SEPARATION). The spent adsorbent is regenerated by stripping with steam or hot gases.

Zinc oxide is effective in removing H₂S, mercaptans, and, to some extent, chlorides. At temperatures above 350 °C, mercaptans decompose to hydrocarbons and H₂S which then reacts with the zinc oxide to form zinc sulfide.



The zinc oxide is sacrificially consumed, being irreversibly converted to zinc sulfide, and the spent bed must be discarded.

Other organic sulfur compounds are not easily removed by either activated carbon or zinc oxide. These compounds can, however, be hydrogenated using hydrogen over a cobalt or nickel molybdenate catalyst. The resulting H₂S can be removed by a conventional zinc oxide bed as described above.

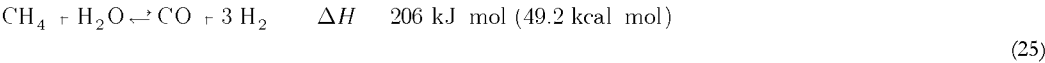
Molybdenum-based catalysts can also be used to hydrogenate olefins that may be present in some natural gases. Whereas olefins are not catalyst poisons in the strictest sense, they can crack or polymerize at high reforming temperatures, blocking the active catalyst sites. The hydrogen for these reactions is either provided by recycling synthesis gas during normal operation, or by cracking ammonia or methanol during start-up, if no external source is available. Details of various process configurations for fixed-bed sulfur removal systems are given in the literature (44).

Fixed-bed desulfurization is impractical and uneconomical if the natural gas contains large amounts of sulfur. In this case, bulk sulfur removal and recovery (qv) in an acid gas absorption–stripping system, followed by fixed-bed residual cleanup is usually employed.

Chlorides may be found in natural gas, particularly associated with offshore reservoirs. Modified alumina catalysts have been developed to irreversibly absorb these poisons from the feed gas.

Some natural gases have also been found to contain mercury, which is a reformer catalyst poison when present in sufficiently large amounts. Activated carbon beds impregnated with sulfur have been found to be effective in removing this metal.

Primary and Secondary Reforming. The conversion of natural gas to synthesis gas in the reforming operation is represented by steam reforming:



and the water–gas shift reaction (eq. 23). Nickel on a refractory or aluminate support catalyzes these reactions; the water–gas shift reaction reaches equilibrium. The overall reaction of the system, equation 25–equation 23, is endothermic and conversion is favored by high temperature, low pressure, and high steam–carbon ratios.

The primary reformer is essentially a process furnace in which fuel is burned with air to indirectly provide the heat of reaction to the catalyst contained within tubes. This area of the furnace is usually referred to as the radiant section, so named because this is the primary mechanism for heat transfer at the high (750–850 °C) temperatures required by the process. Reforming pressures in the range 3–4 MPa (30,000–40,000 atm) represent a reasonable compromise between cost and downstream compression requirements.

Side reactions in the primary reformer are those which form carbon, an undesirable by-product.



Thermal cracking tends to deposit carbon on the catalyst surface which can be removed by steaming. Carbon deposition by this mechanism tends to occur near the entrance of the catalyst tubes before sufficient hydrogen has been produced by the reforming reactions to suppress the right hand side of the reaction. Promoters, such as potash, are used to help suppress cracking in natural gas feedstocks containing heavier hydrocarbons. Carbon may also be formed by both the disproportionation and the reduction of carbon monoxide



Carbon produced by these latter reactions is formed in the catalyst pores, making it much more difficult to remove, and potentially causing physical breakage. Operating steam to carbon ratios are chosen above the minimum required in order to make carbon formation by these reactions thermodynamically impossible (3). Steam is another potential source of contaminants. Chemicals from the boiler feedwater or the cooling system are poisons to the reformer catalyst, so steam quality must be carefully monitored.

The generally accepted catalyst tube material for catalytic reformer designs is centrifugally cast 25% chromium-20% nickel (HK-40) alloy having a specified carbon content of 0.35%–0.45% and providing the optimum combination of strength and weldability. In the 1980s, other materials, most prominently 25Cr-35Ni-Nb (high pressure-modified) alloy, gained acceptance, allowing operation at higher pressures and temperatures while reducing tube wall thicknesses. Thinner walled-tubes result in less stressful operation because of a flatter temperature profile, as well as allowing more volume for catalyst loading. Tubes are generally designed for a minimum theoretical life of 100,000 h, in accordance with API standard 530. Tube failure mode is normally through creep and or stress-rupture (45). Higher reforming pressures are favored, because of the lower energy of compression required for the synthesis loop, smaller vessel sizes, easier CO₂ removal at higher partial pressures, and more efficient process heat recovery.

Available primary reformer designs differ in the arrangement of tubes and burners, tube material, feed gas distribution, and reformer gas collector systems. A primary reformer furnace is a distinguishing feature of an ammonia plant. The radiant section of a typical Kellogg box type steam reforming furnace is shown in Figure 13. In the box reformer the catalyst tubes are arranged in parallel, single-width rows heated from both sides by either gas or liquid fired burners, or both, located in the furnace arch. ICI and Uhde also utilize a top-fire configuration for their primary reformer designs (29,30).

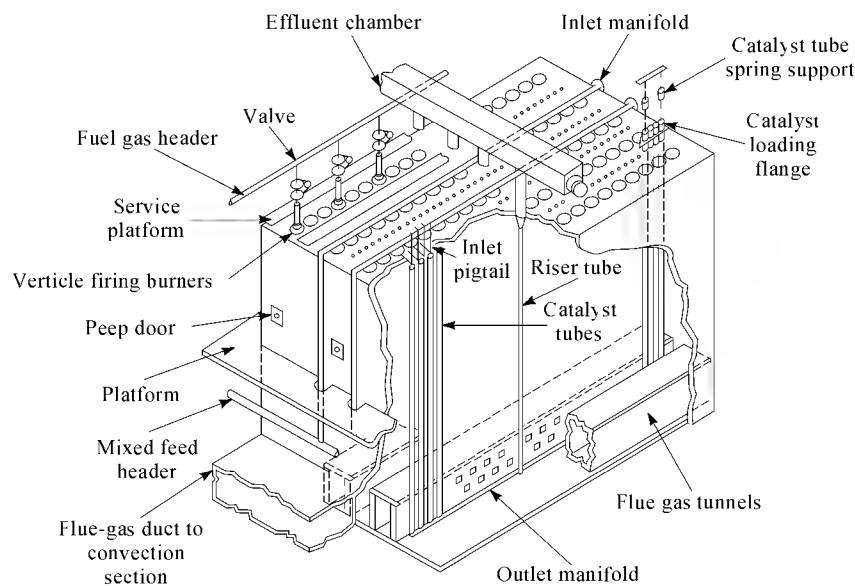


Fig. 13. Radiant section of a Kellogg box-type steam reforming furnace.

In the Haldor-Topsoe primary reformer furnace, the radiant section consists of one or more elongated rectangular furnace cells having vertical catalyst tubes mounted along the center line of the cell in either a staggered double or single straight row. This is a side-fired furnace with flames deflected parallel to the walls which act as radiators. The burners operate satisfactorily on gaseous fuels ranging from hydrogen-rich off-gas to mixtures of vaporized naphtha and steam (46).

In the Foster-Wheeler reforming furnace (3), the inclined terrace walls are vertically and uniformly heated by rising flow of hot gases. The catalyst tubes are heated from both sides and the tube support arrangement uses a carefully designed multiple counterweight system. The lineal burners can operate on both gas and light distillate fuel oil. The radiant box is only about 50% efficient, but the heat liberated and not absorbed by the reforming reaction is recovered in the convection section, allowing overall furnace efficiencies of up to 94%, based on a furnace stack gas temperature of about 150°C for a desulfurized feed.

The practical limit on the primary reformer exit temperature is determined by tube metallurgy considerations. The reforming process is completed adiabatically in the secondary reformer, which is a refractory lined vessel containing a fixed-bed catalyst. The remainder of the endothermic heat requirement is provided by the combustion of part of the primary reformer effluent directly with air within the process itself. Elimination of the mechanical heat transfer surface allows much higher, on the order of 1000°C, process temperatures at the secondary reformer exit to be attained with resulting low methane slips in the range of 0.2–0.3 vol % of dry gas. The secondary reformer catalyst is similar to that used in the primary reformer. It is nickel based, but has an alumina support capable of withstanding higher process temperatures. Because the amount of air added to the secondary reformer is determined by the process nitrogen requirements, the split between the primary and secondary reformers must be in a thermal balance consistent with equipment design temperatures.

Waste Heat Reforming. The primary reformer furnace can be eliminated or significantly reduced in size by utilizing heat available in the secondary reformer effluent or convection section flue gases to provide the heat of reforming. Various process schemes have been proposed, the most promising employing a shell and tube exchanger as the heat transfer device. The ICI Corporation commercialized such a reforming exchanger in an ammonia plant in 1988 as part of their LCA process shown schematically in Figure 14. The reforming exchanger concept has also been applied at the 600 t/d Grodno nitrogen complex in the USSR (47). Figure 15 shows a schematic of an open-tube reforming exchanger design where the secondary reformer effluent flows up countercurrently to natural gas passing through tubes filled with reforming catalyst. The effluents are mixed in a chamber at the end of the tubes and exit on the shell side of the exchanger. Reforming exchangers can offer mechanical simplicity depending on the specific design. Additionally, capital and operating cost savings can be achieved over conventional primary reformer systems.

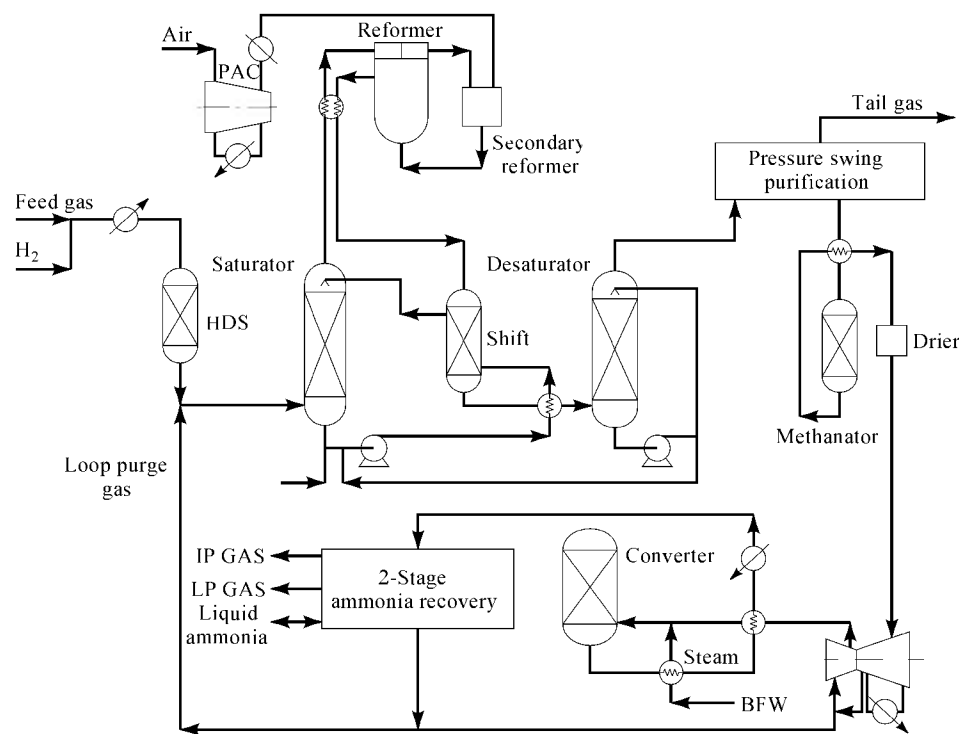


Fig. 14. ICI-LCA process flow sheet; PAC, purified air compressor; HDS, hydrodesulfurization; IP, intermediate pressure; LP, liquefied petroleum; BFW, boiler feed water.

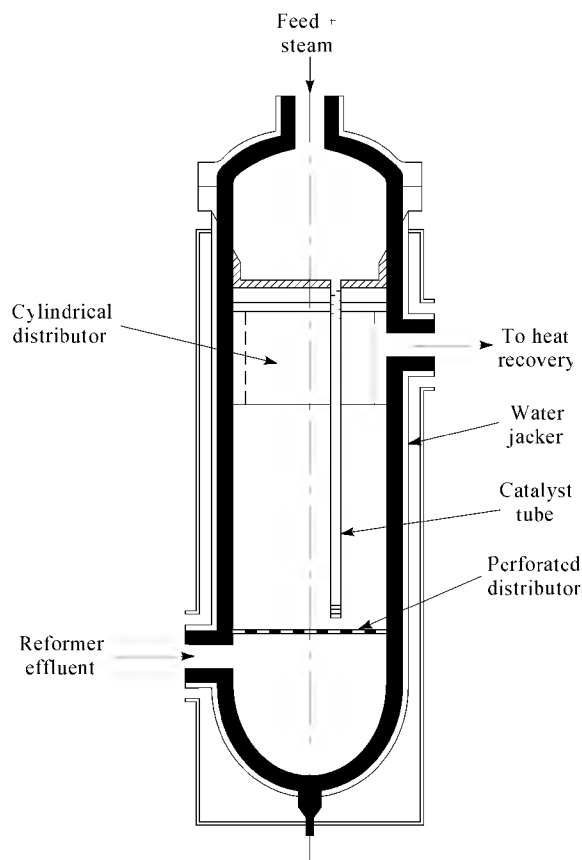


Fig. 15. Kellogg open-tube reforming exchanger.

Shift Conversion. Carbon oxides deactivate the ammonia synthesis catalyst and must be removed prior to the synthesis loop. The exothermic water-gas shift reaction (eq. 23) provides a convenient mechanism to maximize hydrogen production while converting CO to the more easily removable CO₂. A two-stage adiabatic reactor sequence is normally employed to maximize this conversion. The bulk of the CO is shifted to CO₂ in a high temperature shift (HTS) converter operating at 350–400°C to take advantage of the faster reaction kinetics at higher temperatures. The gases are cooled and the remaining CO is shifted to CO₂ in a low temperature shift (LTS) converter to achieve low CO leakages because of the more favorable equilibrium conversion. Alternatively, isothermal shift converters can be used to effectively remove equilibrium constraints (48).

HTS catalyst consists mainly of magnetite crystals stabilized using chromium oxide. Phosphorus, arsenic, and sulfur are poisons to the catalyst. Low reformer steam to carbon ratios give rise to conditions favoring the formation of iron carbides which catalyze the synthesis of hydrocarbons by the Fisher-Tropsch reaction. Modified iron and iron-free HTS catalysts have been developed to avoid these problems (49,50) and allow operation at steam to carbon ratios as low as 2.7. Kinetic and equilibrium data for the water gas shift reaction are available in reference 51.

The low CO leakages of 0.2–0.3 vol % at 200–250°C attainable using LTS converters have allowed the use of downstream methanation to reduce considerably the level of inerts in the make-up gas. The gas at the LTS inlet to the reactor must be over 20°C above its dew point to preclude the possibility of capillary condensation of liquid water within the catalyst.

The LTS catalyst is copper oxide supported on zinc oxide and alumina, and consists mainly of equal parts of CuO, ZnO, and alumina. A start-up circuit is provided to reduce the copper oxide in a new catalyst, using hydrogen, to the active copper metal species. The principal mechanism for deactivation is thermal sintering; the catalyst is poisoned by sulfur and chlorides. Fresh LTS catalyst is highly active, giving a close approach to equilibrium and allowing operation at lower than design temperatures. Gradually raising the temperature to compensate for catalyst aging maximizes catalyst life.

Carbon Dioxide Removal. The effluent gases from the shift converters contain about 17–19 vol % (dry) carbon dioxide (qv) which is ultimately reduced to a few ppm by bulk CO₂ removal, followed by a final purification step. Commercial CO₂ removal systems can be broadly classified as reaction, combination reaction-physical, and physical absorption (qv) systems. The processes generally have an absorber-stripper configuration. Table 8 compares the main features of the various CO₂ removal systems.

Table 8. Acid Gas Treating Processes^a

Process	Solvent	Solution circulation	Acid gas content in treated gas, ppm
<i>Reaction systems</i>			
MEA ^b	20% monoethanolamine	medium	<50
promoted MEA	25–35% monoethanolamine plus Amine Guard	medium	<50
DGA ^c	60% diglycolamine	medium	<100
MDEA ^d	40% methyldiethanolamine plus additives	medium	<50
Vetrocoke	K ₂ CO ₃ plus As ₂ O ₃ -glycine	high	500–1000
Carsol	K ₂ CO ₃ plus additives	high	500–1000
Catacarb	25–30% K ₂ CO ₃ plus additives	high	500–1000
Benfield	25–30% K ₂ CO ₃ plus diethanolamine and additives	high	500–1000
Flexsorb HP	K ₂ CO ₃ amine promoted	high	500–1000
Lurgi	25–30% K ₂ CO ₃ plus additives	high	500–1000
Alkazid	potassium salt of 2-(or 3-) methylaminopropionic acid	^e	^e
<i>Combination reaction-physical systems</i>			

Sulfinol	sulfone and 1.1'-imminobis-2-propanol	medium	<100	
TEA-MEA ^f		high (TEA)	<50	
	triethanolamine and monoethanolamine	low (MEA)		
MDEA–sulfinol–H ₂ O		medium	<50	
<i>Physical absorption systems</i>				
Purisol (NMP)	N-methyl-2-pyrrolidinone	medium	<50	
Rectisol	methanol	medium	<10	
Fluor Solvent	propylene carbonate	g		g
Selexol	dimethyl ether of polyethylene glycol	g		g

^a Ref. 54.

^b MEA is monoethanolamine.

^c DGA is diglycolamine.

^d MDEA is methyldiethanolamine.

^e Dependent on service.

^f TEA–MEA is triethanolamine–monoethanolamine.

^g Dependent on pressure.

Alkanolamine Process. Carbon dioxide is an acidic gas that reacts reversibly with aqueous alkaline solution to form a carbonate adduct. This adduct decomposes upon the addition of low level heat facilitating CO₂ removal. An aqueous solution of 15–20 wt % monoethanolamine (MEA) was the standard method for removing CO₂ in early ammonia plants.

Primary alkanolamine solutions require a relatively high heat of regeneration. Also excessive temperatures or localized overheating in reboilers cause the MEA to decompose and form corrosive compounds. An inhibitor system, such as the Amine Guard system developed by Union Carbide, is an effective method of corrosion control (52). Inhibitors permit the use of higher (25–35%) concentration MEA solutions, thus allowing lower circulation rates and subsequently lower regeneration duty.

Activated tertiary amines such as triethanolamine (TEA) and methyl diethanolamine (MDEA) have gained wide acceptance for CO₂ removal. These materials require very low regeneration energy because of weak CO₂-amine adduct formation, and do not form carbamates or other corrosive compounds (53). Hybrid CO₂ removal systems, such as MDEA–sulfolane–water and DIPA–sulfolane–water, where DIPA is diisopropylamine, are aqueous alkaline solutions in a nonaqueous solvent, and are normally used in tandem with other systems for residual clean-up. Extensive data on the solubility of acid gases in amine solutions are available (55,56).

Activated Carbonate Process. The activated carbonate process is based on absorption of CO₂ by potassium carbonate (57) to give potassium bicarbonate. When the bicarbonate is heated it releases CO₂, regenerating potassium carbonate.

The original hot carbonate process developed by the U.S. Bureau of Mines was found to be corrosive to carbon steel (55). Various additives have been used in order to improve the mass transfer rate as well as to inhibit corrosion. Vetrocoke, Carsol, Catacarb, Benfield, and Lurgi processes are all activated carbonate processes. Improvements in additives and optimization of operation have made activated carbonate processes competitive with activated MDEA and nonaqueous solvent based systems. Typical energy requirements are given in Table 9.

Table 9. Energy Requirements for CO₂ Removal Systems^a

Removal system	GJ mol ^b CO ₂
MEA	210
MEA with inhibitors	140–93
potassium carbonate	107
potassium carbonate and regenerator(s)	88–62
activated MDEA and regenerator(s)	60–42

^a Ref. 57.

^b To convert GJ to G cal, divide by 4.184.

The choice of a specific CO₂ removal system depends on the overall ammonia plant design and process integration. Important considerations include: CO₂ slip required, CO₂ partial pressure in the synthesis gas, presence or lack of sulfur, process energy demands, investment cost, availability of solvent, and CO₂ recovery requirements. Carbon dioxide is normally recovered for use in the manufacture of urea, in the carbonated beverage industry, or for enhanced oil recovery by miscible flooding.

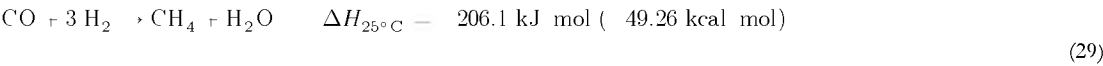
Absorption Systems. Solvents generally perform better at higher partial pressures of carbon dioxide. Because the solubility of acid gases increases as temperature decreases, most absorption systems use supplemental refrigeration to achieve low temperature absorption. Because of the low heat of absorption, the stripping gas is usually air and hence the heat requirement for these processes is negligible. Normally about 70% of the carbon dioxide is recovered by pressure reduction. Higher CO₂ recoveries can be achieved by flashing at high vacuum, or by reintroducing the stripper overheads in the secondary reformer (58).

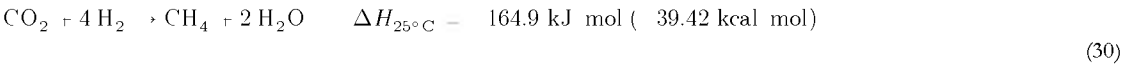
The Rectisol process is more readily applicable for acid gas removal from synthesis gas made by partial oxidation of heavy feedstocks. The solvents used in Purisol, Fluor Solvent, and Selexol processes have low vapor pressures and hence solution losses are minimal. Absorption systems are generally corrosion-free.

Pressure Swing Adsorption. Carbon dioxide can be removed by pressure adsorption on molecular sieves. However, the molecular sieves are not selective to CO₂, and the gases must be further processed to achieve the high purity required for "over the fence" use as in the urea process. Use of pressure swing adsorption for CO₂ removal appears most applicable to small, stand-alone plants (29).

Final Purification. Oxygen containing compounds (CO, CO₂, H₂O) poison the ammonia synthesis catalyst and must be effectively removed or converted to inert species before entering the synthesis loop. Additionally, the presence of carbon dioxide in the synthesis gas can lead to the formation of ammonium carbamate, which can cause fouling and stress-corrosion cracking in the compressor. Most plants use methanation to convert carbon oxides to methane. Cryogenic processes that are suitable for purification of synthesis gas have also been developed.

Methanation. The methanation reactions are the reverse of the reforming reactions





Conversion of the carbon oxides to methane, at the expense of hydrogen, goes almost to completion and the CO and CO₂ content of the treated gas is on the order of a few ppm. A methanator typically operates in the temperature range of 300–400°C. These reactions are strongly exothermic and hence the CO and CO₂ at the inlet to the methanator should be carefully monitored, to avoid temperature runaway.

Most commercial methanator catalysts contain nickel, supported on alumina, kaolin, or calcium aluminate cement. Sulfur and arsenic are poisons to the catalyst, which can also be fouled by carry-over of solvent from the CO₂ removal system.

Dehydration. Use of molecular sieve driers for final clean-up of the carbon oxides and water in the synthesis gas to less than 1 ppm levels has gained prominence in low energy ammonia plant designs. The sieves are usually located at the interstage of the synthesis gas compressor to reduce volume requirements. The purified make-up gas can then be combined with the recycle and routed directly to the converter.

Excess Nitrogen Removal. A number of low energy processes use excess air in the secondary reformer in order to reduce the primary reformer duty. The surplus nitrogen so introduced has to be removed later in the process.

The purifier process shown in Figure 16 incorporates a cryogenic purification step prior to make-up gas compression (59). Methanator effluent is first dried to a very low dew point, then cooled, and expanded in a turbine to liquefy a portion of the gas. After further cooling, the vapor from the partially liquefied stream is scrubbed in a rectifying column to remove all but about 0.2% argon and almost all the methane. About half of the carbon monoxide in the feed after methanation is also removed (see CRYOGENICS). ICI and Uhde process designs utilize a cryogenic separator to remove surplus nitrogen at synthesis loop pressures (29,30). Pressure swing separation is used in various processes to remove excess N₂, CO₂, and part of the methane and argon (47).

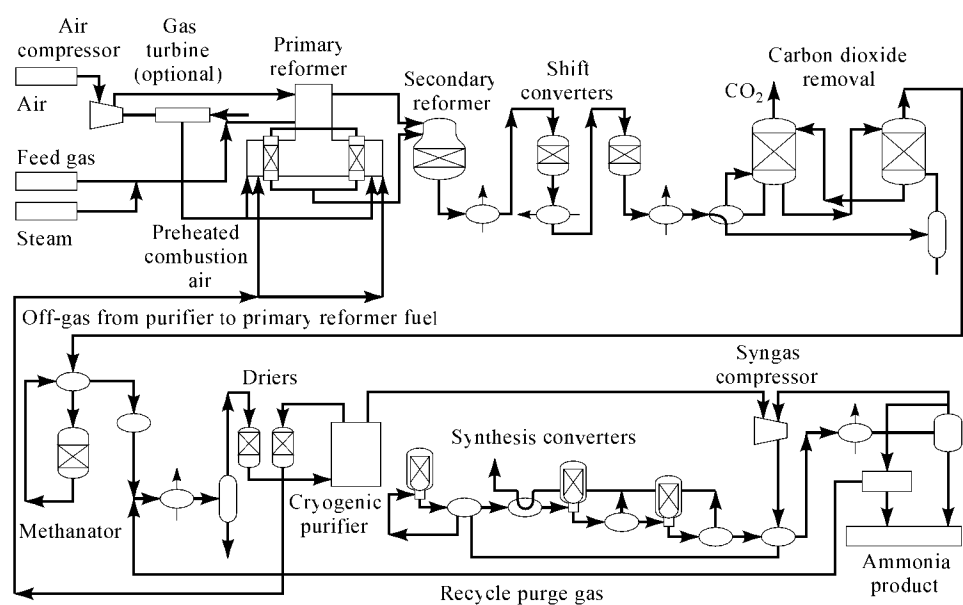


Fig. 16. Flow diagram of the Braun purifier process.

Ammonia Synthesis and Recovery. The purified synthesis gas consists of hydrogen and nitrogen in about 3:1 molar ratio, having residual inerts (CH₄, Ar, sometimes He). The fresh make-up gas is mixed with the loop recycle and compressed to synthesis pressures. All modern synthesis loops recycle the unreacted gases because of equilibrium limitations to attain high overall conversions. The loop configurations differ in terms of the pressure used and the point at which ammonia is recovered.

The kinetic advantages of higher synthesis pressures have already been mentioned, namely, a more favorable equilibrium position and a higher rate of reaction. In addition, at higher pressure ammonia can be recovered by condensation at higher temperatures, thereby reducing refrigeration costs. Plants designed before 1964 operated at pressures up to 34,500 kPa (5000 psi). It has been suggested that lower pressures are favored economically because of the reduction in compression power (60). Modern large tonnage ammonia plants are designed for synthesis pressures of 14,500–15,200 kPa (2100–2200 psi). A greater reduction in synthesis pressures can be achieved without sacrificing ammonia conversion, through the use of high activity synthesis catalysts.

Reciprocating machines satisfied the compression requirements of the early high pressure ammonia plants, but all modern large scale ammonia plants employ centrifugal compressors for synthesis service. Advancements in centrifugal compressor design and efficiency have provided the flexibility and reliability required for a wide range of plant capacities. Normally, centrifugal compressors are driven by steam turbines.

The synthesis loops are generally of two types. The first type recovers ammonia product after make-up gas-recycle compression. In this case the synthesis gas is purified by the washing action that the condensing ammonia has on the make-up gas; however, the disadvantage of this configuration is that it requires a slightly larger compressor wattage because the converter effluent undergoes recycle compression before product condensation. Most modern reduced energy ammonia plant designs employ molecular sieves (qv) as driers at the interstage of the synthesis gas compressor to purify the make-up gas, allowing the synthesis gas to be fed directly to the converter. Ammonia is then recovered downstream of the converter. The molecular sieve loop design lowers the required refrigeration duty, because the converter effluent is not saturated by the make-up gas addition, and this allows some product recovery to be shifted to cooling water. This also lowers the ammonia concentration in the converter feed, resulting in a greater driving force for the ammonia synthesis reaction.

In both arrangements the synthesis gas delivered to the ammonia converter is extremely pure because of the washing action the condensing ammonia has on the incoming make-up gas ridding it of impurities. The result is an extremely long catalyst life, even up to 20 years (54).

In almost all modern plants, the ammonia is recovered by condensation and at modern synthesis pressures, ammonia is usually the source of refrigeration required. In order to maintain a high partial pressure of reactants, inerts entering with the make-up gas are normally removed using a purge stream.

The synthesis converter is the heart of the ammonia plant. Early designs were based on tube-cooling as exemplified by the TVA converter (61). Although these converters offer good thermodynamic operating characteristics, mechanical complexity limits them to small capacity designs. Large capacity ammonia plants in the 1990s exclusively employ multiple bed converters. The range of these converters differ in type of flow (axial, radial, or cross flow), temperature control methodology (quench or indirect cooling), and reaction heat recovery.

In most reactor designs, the cool inlet synthesis gas flows through an annular space between the converter shell and the catalyst cartridge. This flow maintains the shell at low temperatures and eliminates the possibility of hydrogen embrittlement that can occur at normal synthesis pressures. After the gas exits the annular space, it flows to an internally located heat exchanger that preheats the inlet gas to synthesis temperature. Inlet bed temperatures are controlled by quenching the bed effluents with cold synthesis gas. The Kellogg quench converter shown in Figure 17a is a classic example of this reactor configuration.

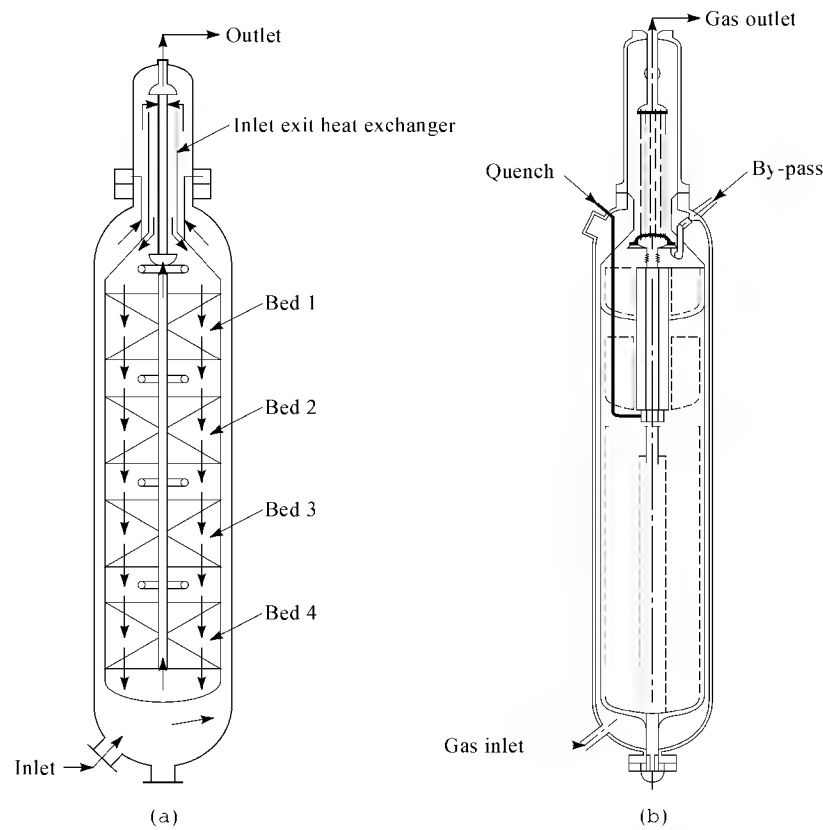


Fig. 17. (a) Kellogg vertical quench converter; (b) Ammonia Casale converter basket modification.

Most modern ammonia converters are designed for radial or cross-flow, and indirect temperature control is provided by a heat exchanger. In the M. W. Kellogg horizontal ammonia converter (Fig. 18), gas flows through shallow longitudinal catalyst beds called slabs contained in an easily removable cartridge. Most of the conversion occurs in the first bed which has the highest driving force to equilibrium. Because of the large cross-sectional flow area, the pressure drop is extremely low even with small catalyst particle sizes. A bypass is provided around the intercooler for temperature control. This converter has been successful for numerous large capacity designs. Radial flow converters, such as those designed by Uhde and Topsoe, offer good gas distribution without the penalty of higher pressure drop. Topsoe's Series 200 radial flow converter is shown in Figure 19 Ammonia Casale's mixed (axial-radial) flow converter offers similar advantages. The C. F. Braun axial flow reactor provides interbed cooling outside the pressure shell as shown in Figure 20. Large capacity ammonia plants employ 3-bed intercooled converters to achieve high ammonia per pass conversions at economical space-time yields.

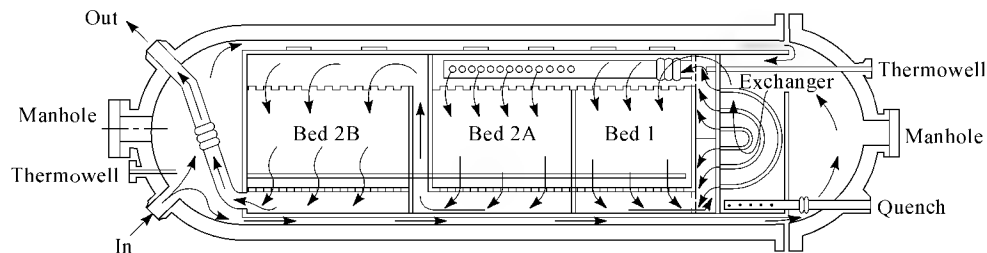


Fig. 18. Kellogg horizontal ammonia converter.

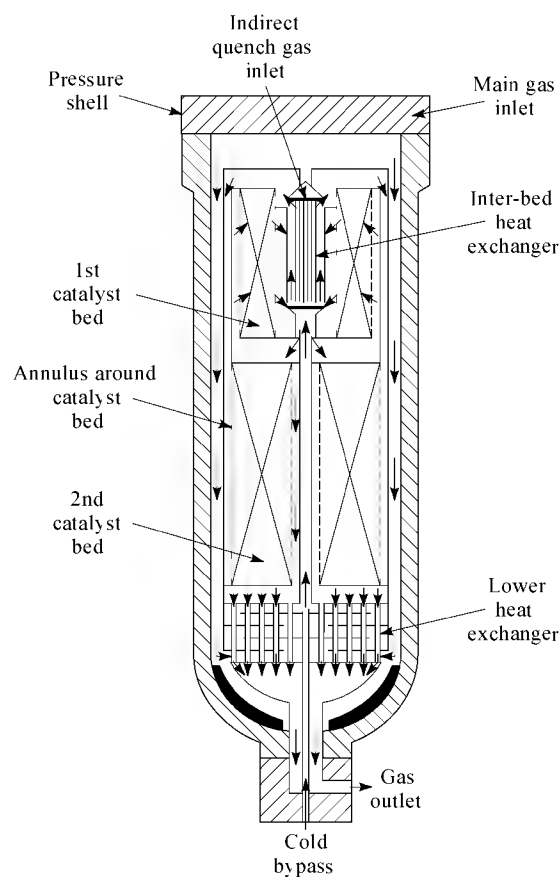


Fig. 19. Topsoe S-200 radial intercooled converter (23).

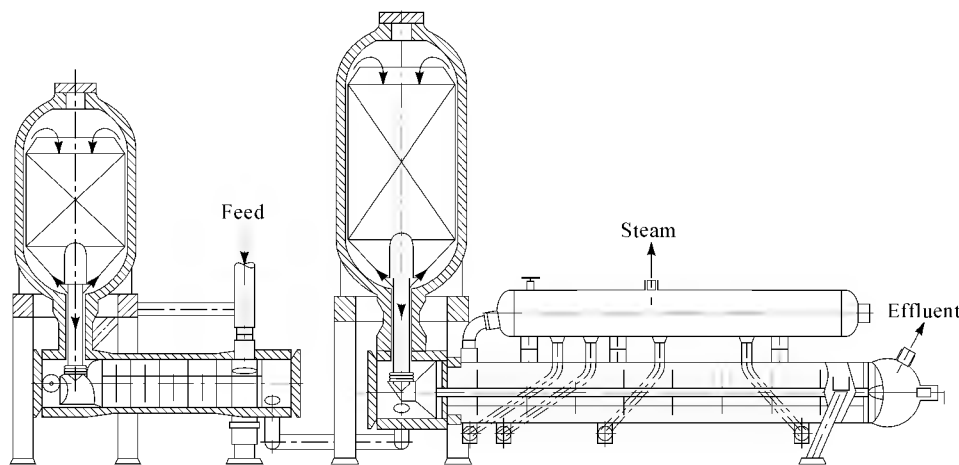


Fig. 20. C. F. Braun ammonia converter system.

Ammonia Plant Modernization. The impetus and justification for debottlenecking older plants are based on ammonia market conditions. Numerous retrofit options are available for capacity increases and or energy savings. Most low energy plant design features such as lower steam to carbon ratios, high efficiency converters, molecular sieve driers, combustion air preheat, hydrogen recovery, and low heat carbon dioxide systems, are also applicable for retrofits (62). Mechanical converter basket modification to radial or split-flow design, coupled with smaller catalyst particle sizes, increases the ammonia conversion per pass while lowering loop pressure drop. Figure 17b shows a typical modification of a 4-bed quench converter to a 3-bed quench-intercooled design, based on Ammonia Casale technology (63). Second generation retrofits based on Kellogg's Advanced Ammonia Process (KAAP) allow ammonia plants with fully utilized converters to achieve significant capacity increases. The high activity KAAP catalyst is integrated downstream of the magnetite catalyst (64).

Advances in process control (qv) technology have resulted in greater operation efficiency for ammonia plants. Distributed control systems (DCS) provide plant operators with more accurate and easier to use real time information. Kellogg's Ammonia Optimizer offers supervisory control of critical parameters such as steam to carbon ratio, hydrogen to nitrogen ratio, and methane leakage. The system allows for continuous optimization of the critical parameters, and can be used to achieve greater ammonia production and or energy savings (65). Enhanced process control results in higher stability in plant operation, and gives the operators easy hands-on control of the plant during emergencies and start-up and shut-down. Investment for instrumentation and control in modern plants accounts for up to 20% of the installed cost.

Purge Gas Recovery. Cryogenic, selective permeable membranes, and pressure swing adsorption units have all been used to recover hydrogen and reject inerts as a means of increasing capacity or energy efficiency. The cost optimization of a particular unit specified in the design or retrofit is a function of loop inert and excess nitrogen level required, plus purity and percentage of recovery streams (66,67). Purge gas recover systems can be customized to recover argon as needed.

Energy Cycle. The ammonia process is characterized by high process temperatures and compression power requirements. The total energy consumption consists of the process feedstock plus utility fuel requirements. Therefore, the energy efficiency of the process is logically maximized by integrating process waste heat recovery and the utility system by means of the Rankine cycle, using steam as the working medium (see POWER GENERATION).

The efficiency of the Rankine cycle itself can be increased by higher motive steam pressures and superheat temperatures, and lower surface condenser pressures in addition to rotating equipment selection. These parameters are generally optimized on the basis of materials of construction as well as equipment sizes. Typical high pressure steam system conditions are in excess of 10,350 kPa (1500 psi) and 510 °C.

Efficient integration of the process with the utility system involves reducing the two principal areas of irreversibility that are inherent in the cycle: the

transfer of process heat to the boiler, and the mixing of saturated boiler liquid with cooler condensate make-up. This strategy is implemented by recovering process heat at the highest possible levels into the motive steam system, and extracting cooler steam at the appropriate level after expansion in a turbine to satisfy process steam and lower level heating requirements.

Selection of the high pressure steam conditions is an economic optimization based on energy savings and equipment costs. Heat recovery into the high pressure system is usually available from the process in the secondary reformer and ammonia converter effluents, and the flue gas in the reformer convection section. Recovery is in the form of latent, superheat, or high pressure boiler feedwater sensible heat. Low level heat recovery is limited by the operating conditions of the deaerator.

A schematic of a typical ammonia plant steam system illustrating these principles is shown in Figure 21. High pressure steam is used exclusively for process drivers. The amount of extraction steam is determined by the process steam requirement for the reformer. The only other process requirement for low level heat is the CO₂ removal system which has been a prime area of improvement for reducing energy input. Export of additional low level heat may be available for offsite use, such as building heating, steam tracing, or desalination units where applicable.

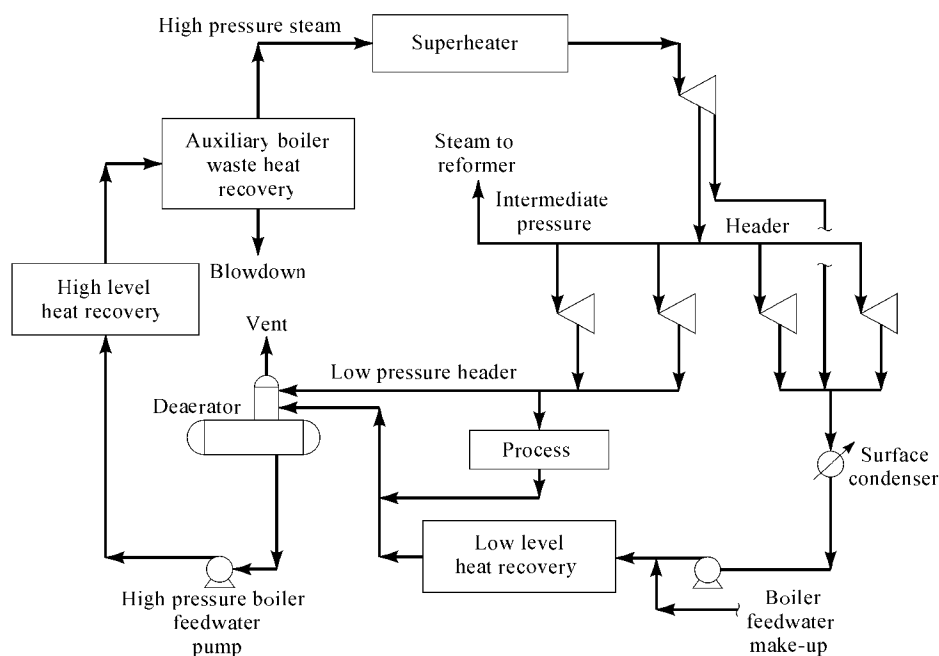


Fig. 21. Kellogg ammonia plant steam system.

A reasonable target for energy minimization is that process requirements dictate fuel firing, with no additional fuel being burned to raise steam. The steam available from waste heat recovery must match the power requirements of the process. Thus careful selection of the process design parameters is needed. In this case, the package or auxiliary boiler firing becomes zero, although this equipment is still included for controllability and start-up. Incremental steam capacity is also convenient for exporting motive steam to other integrated processes, such as urea.

As designs become more efficient with a corresponding reduction in steam requirements, integration with other power cycles becomes feasible. For example, the exhaust from a gas turbine process driver can be used as a source of preheated combustion air for the primary reformer, substantially increasing the efficiency of the conventional Brayton cycle (68). Additional integration options are possible using steam or electricity cogeneration (69). The result in all cases is an improvement in the overall energy cycle.

Environmental Considerations

Ammonia production per se is relatively clean compared to other chemical process industries, and presents no unique environmental problems. Synthesis gas generation is the principal area requiring environmental controls and the nature of the controls depends on the feedstock and method of processing.

Coal feedstocks present the most serious environmental problems. Particulate emissions from the coal handling and processing facilities must be controlled (see *AIR POLLUTION; EXHAUST CONTROL, INDUSTRIAL*). The ash and slag solids removed from the gasification step must be disposed of in an environmentally safe manner. Some gasification produces significant amounts of other liquid by-products such as tars, phenols, and naphthas which must be recovered or incinerated (70). Some coals contain significant amounts of sulfur which must be stripped out of the raw syngas as hydrogen and carbonyl sulfides, necessitating further processing in a sulfur recovery unit (see *SULFUR REMOVAL AND RECOVERY*). Condensate streams from gasifiers may also contain hydrogen cyanide and metals in addition to ammonia complicating disposal further.

Partial oxidation of heavy liquid hydrocarbons requires somewhat simpler environmental controls. The principal source of particulates is carbon, or soot, formed by the high temperature of the oxidation step. The soot is scrubbed from the raw synthesis gas and either recycled back to the gasifier, or recovered as solid pelletized fuel. Sulfur and condensate treatment is similar in principle to that required for coal gasification, although the amounts of potential pollutants generated is usually less (see *COAL CONVERSION PROCESSES, GASIFICATION*).

Reforming of natural gas or naphtha are the cleanest synthesis gas generation operations. Most natural gases contain sufficiently low levels of sulfur that it is possible to remove it in a simple fixed-bed adsorption system. Higher levels of sulfur are amenable to treatment in conventional solvent absorption-stripping systems for acid gas removal, such as MEA. Similarly, organic sulfur compounds in naphtha are hydrotreated over a cobalt-molybdenum catalyst and stripped as hydrogen sulfide. Residual sulfur is removed in a fixed-bed system similar to that used for natural gas before reforming.

Process condensate from reforming operations is commonly treated by steam stripping. The stripper is operated at a sufficiently high pressure to allow the overhead stripping steam to be used as part of the reformer steam requirement (71). Contaminants removed from the process condensate are reformed to extinction, so disposal to the environment is thereby avoided. This system not only reduces atmospheric emissions, but contributes to the overall efficiency of the process by recovering condensate suitable for boiler feedwater make-up because the process is a net water consumer.

Incorporation of a feed gas saturator coil in the convection section of the primary reformer allows for 100% vaporization of the process condensate. The steam is used as process steam in the reformer.

All fired equipment, whether it be a process furnace or a utility boiler, is also subject to regulation, usually in the form of sulfur and nitrous oxide limitations. These flue gases can be suitably treated by a combination of conventional control techniques including low NO_x burners, selective catalytic reduction, and flue gas scrubbing. Effluents from other utility systems, such as blowdowns from steam drums, cooling water systems and polisher regenerates, can normally be handled by neutralization and holding ponds (see *AIR POLLUTION CONTROL METHODS*).

Federal regulations (72) administered by the EPA establish limitations on the ammonia in aqueous effluents on a site-specific basis. The range of values is 0.05–0.1875 kg of ammonia (as nitrogen) per ton of product on a maximum daily basis; corresponding 30-day average values range from 0.025 to

0.0625 kg ammonia (as nitrogen) per ton of product. Generally, the pH of the effluent must be between 6 and 9.

Storage, Shipping, and Handling

Storage. Anhydrous ammonia is ordinarily stored in refrigerated tanks at the plant site at -33.3°C and atmospheric pressure. The need to store large quantities of ammonia results from the seasonal nature of the ammonia fertilizer market. Cylindrical tanks of large (27,000–50,000 t) capacities, either of single-walled or double-walled construction, have been installed in primary market areas (73). So-called double-integrity tanks have been designed having a secondary containment feature for added safety (74). Ammonia evaporating to maintain the necessary low temperatures must be vented. The vented gas is relieved for recycle or absorbed in water to make aqua ammonia.

Relatively small quantities of anhydrous ammonia are stored in spherical vessels at pressures above 275 kPa gauge (40 psig) and ambient temperature. Not more than 189 m³ (50,000 U.S. gal) of ammonia should be stored in an unrefrigerated tank (75). Storage tanks must not be filled to more than 56% of the water weight capacity of the container at 15°C (76). There is a tendency to design foundations for the weight of the tank filled with water to hydrostatically test the tank completely. Tanks should be built of steel, and designed for a minimum working pressure of 1724 kPa gauge (250 psig).

Pressurized storage tanks are provided with spring-loaded relief valves and atmospheric storage tanks with combination pressure-vacuum valves. Relief valve pressure settings must not exceed the design working pressure of the tank. Double-walled storage vessels have an additional relief system: an inert gas, nitrogen, is used to maintain a slight positive pressure in the annular space to prevent air and moisture from entering and corroding metal surfaces and damaging insulation. Therefore, safety valves are used for overpressure protection of the annular space. Emergency discharges from relief valves are piped to a stack which is at least 1.83 m above any surrounding platform or working area. Silencers are provided for all relief valves.

Refrigerated storage tanks are insulated using great care to minimize heat loss and access of air and moisture to the insulation or metal surface. In double-wall tanks, the annular space is usually filled with perlite and the external surface of the outer tank is painted for corrosion protection.

Shipping. Distribution of anhydrous ammonia in the United States is facilitated by pipeline, where three companies serve 11 states having lines almost 4800 km in total length, by water, where over 4800 km of river barge transport capability exists, by rail, where an extensive network in the continental United States has tie-ins to Canada and Mexico, and by truck, used mainly for interstate or local delivery.

The Mid-America Pipeline System (MAPCO) (77) for ammonia transportation contains 1763 kilometers of 101 mm, 152 mm, and 203 mm pipe having a pumping capacity of 3885 metric tons per day and supporting terminal storage facilities. Peak delivery from the system is 4,216 metric tons per day.

The Gulf Central Pipeline system (78) contains 3220 km of 152 mm, 203 mm, and 254 mm pipe and has a pumping capacity of 2545 metric tons per day and supporting terminal storage facilities. The Tampa Bay Pipeline network services several ammonia plants along a 133 km route.

Capacities for trucks and rail cars are normally 100–150 m³. Barges can usually accommodate from 400–2000 t.

All ammonia piping should be standard (Schedule 40) or extra heavy (Schedule 80) steel having welded or screwed joints, respectively. Galvanized piping or brazed joints should never be used. Ammonia accepted for pipeline transportation must meet the following specifications: NH₃, 99.5 vol % min; dissolved inerts, 0.16% max, oil, 5 ppm max; and water, in the form of steam condensate, 0.2% min, or distilled water, 0.5% max.

Pipeline systems for transporting anhydrous ammonia that are urea and ammonium nitrate (UAN) and LNG compatible, exist in Europe, Mexico, and the Soviet Union. Export-oriented ammonia producing countries utilize huge ocean-going tankers that contain up to 50,000 t for distribution of ammonia. Co-shipment in refrigerated LNG tankers is usually done.

Handling. Gasket material most suitable for anhydrous ammonia services is hard finished, rubber-frictioned asbestos (qv) sheet. Use of asbestos-based materials is under Federal review. Aluminum has been applied satisfactorily as a gasket material for flat-faced and grooved flange joints, but is not generally recommended. Rubber rings are not recommended. For special applications, lead may be used.

Magnetic or rotary gauges are preferred to gauge glasses. Ammonia should never be closed into a gauge glass: an increase in pressure may break the glass. Glasses should be protected by a guard in case of breakage, should have excess flow valves to stop ammonia flow if breakage occurs, and should have automatic self-closing shutoff valves which must be held open to take a reading.

Pressure reducing valves should be of steel construction, designed for minimum and maximum operation conditions. Pressure gauges should be of all-iron construction. Pressure relief valves should be of the spring-loaded type. Rupture disks may be used only as auxiliary equipment. Differential pressure measurements using mercury manometers should be avoided in ammonia service.

Hoses must be made for anhydrous ammonia service 2500 kPa (348 psig) working pressure and stamped for this service. In locations where hoses may be abraded, wire braid armored or reinforced hose types should be used. Hose ends should have boss or other acceptable all iron ferruled couplings.

Ammonia is corrosive to alloys of copper and zinc and these materials must not be used in ammonia service. Iron or steel should usually be the only metal in ammonia storage tanks, piping, and fittings. It is recommended that ammonia should contain at least 0.2% water to prevent steel stress corrosion. Mercury thermometers should be avoided.

Leaks can be detected at once by ammonia odor unless there is already an appreciable amount of ammonia in the air. Leaks can be exactly located by using either moist phenolphthalein paper or an open bottle of hydrochloric acid. If a serious ammonia leak is discovered, a large column of water applied through a fire hose having a spray nozzle can be used to absorb the vaporized ammonia.

Economic Aspects

Capacity, Production, and Consumption. Ammonia production has worldwide significance: about 85% of the ammonia produced is used for nitrogen fertilizers. As the primary source of fertilizer nitrogen, it is key to solving world food production requirements. The remaining 15% goes into various industrial products such as fibers, animal feeds, explosives, etc.

Until the 1960s ammonia production occurred on a small scale, served local markets, and used a wide range of feedstocks. Technological changes and inexpensive natural gas feedstock became available during the 1960s such that production costs were lowered and fertilizer consumption grew rapidly, starting the so-called green revolution. Growth in the global ammonia capacity and fertilizer nitrogen consumption are shown in Table 10. Fertilizer nitrogen use, which grew at an annual compounded rate of 11.5% in 1960–1970 and 6.7% in the 1970–1980 period, slowed to 3.8% in the 1980s. It is projected to grow at less than 3.0% in the 1990s.

Table 10. Global Ammonia Capacity and Fertilizer Nitrogen Consumption, 10⁶ t of Elemental Nitrogen^a

Year	Ammonia nominal capacity	Fertilizer consumption
1960	16.23	9.54
1970	50.64	28.17
1980	101.58	57.19
1990	119.57	80.30

^a Refs. 79, 80.

Geographical distribution of the world ammonia capacity is given in Table 11. Through most of the 1970s, North America, primarily the United States, and Western Europe were the focal points for ammonia capacity. However, in the 1980s the USSR overtook the United States in ammonia capacity and in 1990 was the world's largest producer. China is the world's second largest producer and significant increases in ammonia capacity have also occurred in India, Mexico, Indonesia, and the Middle East. Essentially all of the capacity increases, whether in developing countries or elsewhere, have resulted from the use of the technology that was introduced in the 1960s in the United States.

Table 11. World Ammonia Capacity Distribution

Region	Percentage	
	1975 ^a	1990
Africa	2.1	3.0
Asia	25.9	35.4
Latin America	3.9	5.3
North America	21.4	13.8
Eastern Europe	12.8	9.7
Western Europe	18.8	11.3
USSR	15.1	21.5

^a Ref. 80.

Since the 1960s global ammonia supply and demand positions have fluctuated mainly from balanced to surplus. An exception was in 1974 when there was a world shortage of ammonia. Table 12 shows the ammonia supply and demand balances for 1986, 1988, and the projected situation for 1991 (81). In going from nominal or nameplate capacity to ammonia supply capability, capacity utilization factors from region to region that are below nameplate production are taken into account. Examples of capacity utilization factors are maintenance capabilities, influence of infrastructure, and lower capacity utilization during the first three years of a new plant. These can range from 95° in North America and Western Europe to 80° in Asia and North Africa. Industrial use of ammonia amounts to about 11° of production. Conversion loss of up to 8° has been estimated in going from ammonia to products used at the farm level. The resultant ammonia available for fertilizer nitrogen is then adjusted by nitrogen (N) supplies from other sources, eg, Chilean nitrate, and gives an estimate of total fertilizer nitrogen supply. The actual fertilizer consumption of N compared to total supply shows a surplus for 1986 and 1988, and is projected to be in balance in 1991.

Table 12. World Ammonia Supply and Demand, 10⁶ t of Elemental Nitrogen

Production and use	1985–1986	1987–1988	1990–1991 ^a
nominal capacity	110.85	114.15	119.18
supply capability (production)	90.60	93.80	98.84
industrial use	10.28	10.55	10.93
losses	7.60	7.92	8.40
available for fertilizer	72.72	75.33	79.51
non-NH ₃ nitrogen supply	0.56	0.56	0.56
total fertilizer nitrogen supply	73.28	75.89	80.07
total fertilizer consumption	64.98	73.46	80.11
surplus (deficit)	8.30	2.43	0.06

^a Preliminary figures.

It should be noted that a significant increase in ammonia supply could be achieved by improving the on-stream efficiency of plants and avoiding excessive losses throughout the downstream conversion and distribution processes.

Markets. Industrial use of ammonia varies according to region. For example, industrial usage represents 20° of the ammonia production in the United States and Western Europe, 10° in the USSR, 1–10° in Asia, and 5° in Latin America and North Africa (79). Fertilizer ammonia consumed domestically in most countries is converted to straight or compound fertilizers such as urea , ammonium nitrate, diammonium phosphate, and various grades of mixed fertilizers. However, almost 29° of ammonia nitrogen in the United States is consumed as direct application material. The use of nitrogen solution such as urea and ammonium nitrate (UAN) has also become popular in the United States and the USSR.

Even though a global ammonia over-supply existed during the 1980s, there are still significant regional production deficiencies, especially in China, India, South America, and sub-Saharan Africa. These regional deficiencies mean significant worldwide trade. In 1984, world trade of ammonia and urea amounted to 7.0 and 11.18 million metric tons of N, respectively (82). Ammonia is usually transported by refrigerated ships; urea is shipped either in bulk or bagged material. The largest exporter of ammonia is the USSR (34°); the largest importer is the United States (34°). The largest exporters of urea are the USSR and Romania (43°); and China, the United States, and India are the largest importers (62°).

Manufacturing Cost. Table 13 provides a breakdown of the estimated manufacturing cost of ammonia in a 1000 metric tons per day plant built in early 1990 on the U.S. Gulf Coast. The fixed investment includes off-sites, consisting of raw water and boiler feed water treatment, ammonia storage, and a cooling tower. The working capital includes product storage for 30 days at \$150 t. Natural gas is feedstock to a reduced energy ammonia process commercialized in the early 1980s. The 20° pretax return on investment is a reasonable expectation for plants located in Western economies, where corporate tax on earnings is about 50°.

Table 13. Estimated Ammonia Manufacturing Cost^a

Factor	Unit rate t	\$US units	Cost, \$ t
<i>Variable costs</i>			
natural gas (feed-fuel), GJ ^b	28.45	1.90	54.06
boiler feed water make-up, m ³	1.1	0.25	0.28
cooling water circulation, m ³ (Δ temperature 10° C)	210	0.01	2.10
catalyst cost			1.7
<i>Fixed costs^c</i>			
labor, personnel shift (\$10 h)	6	10	1.44
supervision, 100° of labor			1.44
interest on working capital, °	10		1.30
indirect charges, ° ^d	16		44.06
<i>Total production cost</i>			106.38
pretax return on investment (ROI), °	20		55.07
ammonia cost (FOB plant)			161.45
cash cost of production ^e			78.84

^a Reduced energy ammonia process utilizing natural gas feed at a U.S. Gulf Coast location. Daily production of 1,000 t, yearly production of 345,000 t, and

total investment of \$99,500,000 (U.S. \$95 million in fixed investment and \$4.5 million in working capital).

^b To convert GJ to Gcal, divide by 4.184.

^c Fixed investment includes cooling tower, boiler feedwater treatment, raw water ammonia storage as minimum off-sites requirement.

^d Indirect charges are 16% of fixed investment per ton per year: 10% depreciation; 1.5%, insurance; 3%, maintenance (labor, materials); 1.5%, general sales and marketing.

^e Cash cost excludes 10% depreciation allowance and 20% pretax ROI.

As can be seen from this analysis, the natural gas feedstock and capital charges amount to over 93% of the total production cost before return on investment. Therefore, energy consumption and capital investment are the key factors in determining ammonia production profitability. A natural gas delivered price of \$1.90/GJ (\$2.00/MMBtu), on lower heating value (LHV) basis, was reported for February 1990 in the United States (81). Obviously, different natural gas prices change the economics. Location of the ammonia plant influences the fixed investment and can be substantially higher if a complete grassroots plant in a country lacking the necessary infrastructure is built. In the energy-rich countries of the Near East, in the USSR, and in North Africa, natural gas prices are on the order of \$0.47/GJ (\$0.5/MMBtu); however, construction cost at these locations tends to be higher than on the U.S. Gulf Coast.

Whereas the manufacturing cost is strongly influenced by energy prices, cost of money, and capital investment, ammonia selling prices are usually determined by supply and demand. Therefore, the profitability of ammonia plants is determined by the margin between cost of production and ammonia price.

Table 13 shows an estimate of the cash cost of ammonia of \$78.84/t. The FOB price of ammonia on the U.S. Gulf Coast in late February 1990 was \$107/t (81). Therefore, a producer in Louisiana, Florida, or Texas could have a \$28 margin at a natural gas price of \$1.90/GJ (\$2.00/MMBtu) and energy consumption of \$28.45/GJ/t (24.5/MMBtu/ST). However, the plants on the U.S. Gulf Coast were built in the late 1960s and early 1970s and consume on the order of 34.85/GJ/t (30/MMBtu/ST), which gives about \$12.00/t higher production cost or a margin of only \$16/t.

Pricing. Ammonia prices are expected to rise in the 1990s as oversupply is gradually decreased. But in the past ammonia prices on the U.S. Gulf Coast have dipped as low as \$66–77/t, below the cash cost of production in the most efficient large capacity plants. Smaller plants and those using more energy were operating at substantial losses and were forced to close or to shut down and import ammonia from such places as Mexico, Trinidad, Venezuela, and the USSR.

Other factors that affect either production cost or the consumption of fertilizers tend to be periodic and short-lived. On the consumption side, weather conditions, prices of fertilizers, and the political stability of a region influence demand. The supply side is influenced by raw material availability, reliability of infrastructure, on-stream efficiency, age of plants, and the construction or modernization of existing plants.

Ammonia and urea prices from 1968 to 1986 are shown in Figure 22 (82). The average FOB price of ammonia on the U.S. Gulf Coast in early 1991 was \$105/t.

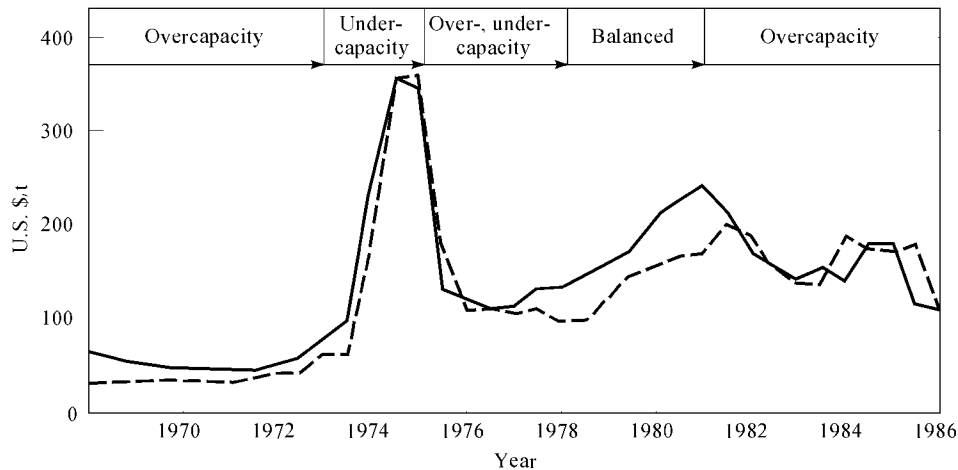


Fig. 22. Ammonia and urea prices, 1968–1985. —, ammonia prices, F.O.B. (Western Europe); —, urea prices, F.O.B. (Western Europe) bagged.

During 1968–1973 there was an overcapacity of ammonia resulting in a depressed market. In the following years demand for nitrogen fertilizers surpassed available supply and as a consequence prices started to rise. Skyrocketing prices in 1974 were largely the result of the 1973 oil embargo and prices returned to \$100–125/t in 1975 and 1976, which were more in line with production costs. However, the fluctuating supply started an upward trend in ammonia and urea prices in 1977, which was reinforced by the 1978 oil embargo. The latter part of the 1970s also saw considerable capacity expansions in the United States, Mexico, China, Indonesia, and by 1981 existing capacity was greater than required. The fall in ammonia and urea prices that followed was a direct result of overcapacity in the 1980s and the shifting of production from high to low cost energy areas.

Transportation and Distribution Cost. Although much ammonia serves as feedstock for other processes, the largest single use in the United States is as a direct application fertilizer without further processing. This direct application consumption is mostly in the farm belt and ammonia produced in the Gulf Coast states is shipped to terminal facilities and then distributed by retail outlets to the farmer.

Ammonia is usually transported for long distances by barge, pipeline, and rail, and for short distances by truck. Factors that govern the type of carrier used in anhydrous ammonia transportation systems are distance, location of plant site in relation to consuming area, availability of transportation equipment, and relative cost of available carriers. Typical costs (83) of pipeline, barge, and rail modes for long distance transport are \$0.0153, \$0.0161, and \$0.0215 per ton per kilometer, respectively, for distances of about 1600 km. Short distance truck transportation costs (83) are much higher. Costs are typically \$0.0365/(t·km) for distances on the order of 160 km.

Because of the nature of the industry, agricultural ammonia consumption is cyclic. During the Spring fertilizer season, about 75% of the dedicated production is sold.

To reduce storage costs involved in such a cyclic consumption pattern, there has been substantial growth in the erection of large refrigerated anhydrous ammonia storage terminals at key points within large marketing areas. Terminal cost (84) is reported to add typically about \$11.00/t.

In the United States most liquid and solid fertilizers are supplied to the farmer by retail fertilizer dealers. Because of the highly seasonal nature of the business, marketing cost can be high. In an effort to spread overhead costs over a broader base, retail dealers diversified into other farm products such as seed, pesticides, and farm equipment. In a study of 47 U.S. Midwestern retail fertilizer firms (1974 financial data) (85), using an average ammonia mark-up cost ranging from about \$47.40/t to \$91.50/t was reported for the least and most profitable firms studied, respectively. Inventory position and supply arrangements were reported to be the most significant factors in affecting profitability.

Ammonia in the world trading markets costs on the order of \$35/t to ship between the United States and Western Europe.

Specifications and Analysis

Anhydrous and aqua ammonia are manufactured in various grades depending on use. Specifications are given in Tables 14 and 15, respectively.

Table 14. Anhydrous Ammonia Specifications^a

Material content	Commercial or fertilizer grade	Refrigeration grade	Metallurgical grade
ammonia, min wt %	99.5	99.98	99.99
water, max ppm by wt	5000	150	33
oil, max ppm by wt	5	3	2
noncondensable gases, max mL/g		0.2	10

^a Ref. 31.

Table 15. Aqua Ammonia Specifications^a

Grade	Ammonia, wt %
<i>United States Pharmacopeia</i>	
stronger ammonia water	28–30
ammonia test solution	9.5–10.5
normal (1 N) aqua ammonia	1.7
chemically pure	28
technical, B ₁₅ ^o ^b	
26	29.4
16	10.3
18	14
20	
	17.75

^a Refs. 87, 88.

^b Be° degree Baume°; specific gravity 145 (145–Be°).

Anhydrous ammonia is normally analyzed for moisture, oil, and residue. The ammonia is first evaporated from the sample and the residue tested (86). In most instances, the amount of oil and sediment in the samples are insignificant and the entire residue may be assumed to be water. For more accurate moisture determinations, the ammonia can be dissociated into nitrogen and hydrogen and the dewpoint of the dissociated gas obtained. This procedure works well where the concentration of water is in the ppm range. Where the amount of water is in the range of a few hundredths of a percent, acetic acid and methanol can be added to the residue and a Karl Fischer titration performed to an electrometrically detected end point (89–92).

Oil can be determined by extracting the residue using carbon tetrachloride and then evaporating the CCl₄. Sediment such as iron is determined by dissolving in hydrochloric acid followed by colorimetric estimation. Dissolved noncondensable gases are determined by analyzing the atmosphere above the liquid ammonia.

Gas streams can be analyzed for ammonia by bubbling a measured quantity of the gas through a boric acid solution to absorb the ammonia. The solution is then titrated against sulfuric acid. This analysis is applicable only if other constituents in the gas stream do not react with boric acid.

Ammonia and ammonium ions in industrial water streams, including waste-water streams, can be determined by either of two methods (ASTM Procedure D1426). In the first, the sample is buffered to a pH of 7.4 and distilled into a solution of boric acid where the ammonia nitrogen is determined colorimetrically with Nessler reagents or titrated using standard sulfuric acid.

The other method is less accurate but more rapid and involves direct Nesslerization of the sample for colorimetric determination. Other colorimetric indicators with more sensitivity, such as indophenol, have been used in place of Nessler's reagent. Ion-selective electrodes have also found use in analysis for trace ammonia (93).

Health and Safety

Ammonia is a strong local irritant which also has a corrosive effect on the eyes and the membranes of the pulmonary system. Vapor concentrations of 10,000 ppm are mildly irritating to the skin, whereas 30,000 ppm may cause burns. The physiological effects from inhalation are described in Table 16. Prolonged, intentional exposure to high levels of ammonia is unlikely because its characteristic odor can be detected at levels as low as 1–5 ppm (94). The real danger occurs when escape is impossible, or the exposure victim has lost consciousness.

Table 16. Physiological Effects of Ammonia^a

Concentration, ppm	Effects
20–50	perceptible odor
40–100	eye and respiratory system irritation
400–700	severe eye and respiratory irritation; potential for permanent damage
1,700	convulsive coughing and bronchial spasms; half four exposure potentially fatal
5,000–10,000	death from suffocation

^a Ref. 97.

Ammonia is generally not considered to pose a serious fire or explosion hazard. However, although ignition is difficult, it is not impossible as proved by an explosion resulting from a leak in an indoor ammonia refrigeration system (95). Ammonia does not produce unstable or hazardous decomposition products. However, contact with calcium, gold, mercury, silver, or chlorates may result in explosive compounds.

Current OSHA standards specify the threshold limit value (TLV) 8-h exposure to ammonia as 50 ppm (35 mg m⁻³). However, the ACGIH recommends a TLV of 25 ppm (96). Respiratory protection should be provided for workers exposed to ammonia. Protective clothing such as rubber aprons, boots, gloves, and goggles should be worn when handling ammonia.

Uses

Table 17 gives a breakdown of ammonia uses in the United States for 1986. The primary use is in the fertilizer industry which also determines ammonia demand.

Table 17. 1986 Markets for Ammonia in the United States^a

Use	Market, %
fertilizer	
direct application	28.7
urea	22.4
ammonium nitrate	15.8
ammonium phosphates	14.6
ammonium sulfate	3.4
nitrogen solutions and mixed fertilizers	0.6
<i>Total</i>	<i>85.5</i>
industrial	
commercial explosives	4.1
fibers—plastics	5.1
<i>Total</i>	<i>9.2</i>
other	5.3

^a Ref. 31.

Fertilizers. The fertilizer industry constitutes the largest market for ammonia and direct application of anhydrous ammonia represents the largest single consumption. Some of the advantages (98) of anhydrous ammonia are: (1) Having 82% nitrogen, it is the most concentrated nitrogen fertilizer available. (2) It improves soil tilth, increasing the water-holding capacity, and decomposes crop residue and organic matter. (3) It is applied 150–200 mm deep or at plow depth, expanding laterally to form a band measuring about 200 mm wide. Applied in the form of a slug, or mass, this increases the efficiency for great uptake of nitrogen by crop root. It increases the number, size, and strength of crop roots resulting in deeper penetration, greater plant development, and ability to withstand periods of drought. (4) It is easy to apply; it flows under its own pressure from the applicator tank to the soil. (5) It combines with clay and organic matter to resist leaching losses. (6) It can be applied at various times, fall, winter, or spring as a pre-plant, or in the summer as a sidedress application. (7) It releases other plant food elements that are present in the soil, such as potassium, phosphorus, calcium, and magnesium.

Ammonia is also the primary building block for downstream manufacturing of a wide range of fertilizer products. Table 18 gives the relative amounts of ammonia used for the manufacture of these nitrogen products.

Table 18. Ammonia Use for Production of Nitrogen Fertilizers^a

Product	Raw material	Raw material used, (ton per ton of product)
urea	ammonia	0.58
nitric acid	ammonia	0.29
ammonium nitrate	ammonia	0.21
	nitric acid	0.77
nitrogen solutions ^b	urea	0.33
	ammonium nitrate	0.41
ammonium sulfate	ammonia	0.27
ammonium phosphate ^c	ammonia	1.29

^a Ref. 31.

^b Based on UAN-30.

^c Per ton of contained nitrogen.

Ammonia and nitric acid are the two basic ingredients in the manufacture of ammonium nitrate. In addition to consuming ammonia directly, the manufacture of ammonium nitrate consumes ammonia by way of nitric acid production. The largest single use of nitric acid is that of ammonium nitrate production (see AMMONIUM COMPOUNDS). Urea (qv) is manufactured by reacting ammonia and carbon dioxide. Urea manufacturing facilities are often located close to ammonia plants.

Ammonia is consumed in the manufacture of ammonium phosphates and ammonium sulfate by reaction with phosphoric acid and sulfuric acid, respectively. The phosphates may contain ortho- and polyphosphate values. Ammonium sulfate is also a by-product from other ammonia-using industries such as caprolactam (qv) and hydrogen cyanide (see CYANIDES).

Nitrogen solutions consist of fertilizer product combinations, eg, ammonium nitrate–ammonia, urea–ammonium nitrate–ammonia, urea–ammonium nitrate, and urea–ammonia solutions. Mixed fertilizers cover a broad range and can be loosely defined as fertilizers which contain chemically mixed nitrogen, phosphorus, and potassium (N–P–K). Examples are ammonium phosphate–potash mixtures and ammonium phosphate nitrates.

Industrial. Nitric acid is itself the starting material for ammonium nitrate, nitroglycerin [55-63-0], trinitrotoluene [118-96-7], nitrocellulose [9004-70-0], and other nitrogen compounds used in the manufacture of explosives (see EXPLOSIVES AND PROPELLANTS). Nitric acid is made by oxidation of ammonia to nitrogen dioxide [10102-44-0] which is subsequently absorbed by water.

Ammonia is used in the fibers and plastic industry as the source of nitrogen for the production of caprolactam, the monomer for nylon 6. Oxidation of propylene with ammonia gives acrylonitrile (qv), used for the manufacture of acrylic fibers, resins, and elastomers. Hexamethylenetetramine (HMTA), produced from ammonia and formaldehyde, is used in the manufacture of phenolic thermosetting resins (see PHENOLIC RESINS). Toluene 2,4-diisocyanate (TDI), employed in the production of polyurethane foam, indirectly consumes ammonia because nitric acid is a raw material in the TDI manufacturing process (see AMINES; ISOCYANATES). Urea, which is produced from ammonia, is used in the manufacture of urea–formaldehyde synthetic resins (see AMINO RESINS). Melamine is produced by polymerization of dicyanodiamine and high pressure, high temperature pyrolysis of urea, both in the presence of ammonia (see CYANAMIDES).

Less importantly, ammonia is used: (1) As a refrigerant in both compression and absorption systems (see REFRIGERATION AND REFRIGERANTS). Ammonia's high latent heat, low vapor density, chemical stability, and low corrosion to iron parts promote its use in large industrial installations. (2) In the pulp and paper industry for the pulping of wood and as a dispersant for casein in the coating of paper (see PAPER; PULP). (3) In the metal industry for detinning of scrap metal, in the extraction of certain metals, eg, copper, nickel, molybdenum, and tungsten from their ores, in metal treating where cracked (dissociated) ammonia is used as a reducing atmosphere for the bright annealing of stainless steels, nickel and its alloys, for the reduction of metal oxides and for the nitriding of steels for case-hardening (see METAL TREATMENTS). (4) As a medium to reduce nitrogen oxides in stack gases. Both catalytic and noncatalytic systems have been developed. (5) As a modifying reagent in the flotation of phosphate ores, and as collecting reagents for the froth flotation

of a wide range of minerals. (6) As a corrosion inhibitor at petroleum refineries and natural gas plants and to neutralize the acid constituents of oil, thereby protecting refinery equipment (see CORROSION AND CORROSION INHIBITORS). (7) In the rubber industry for the stabilization of natural and synthetic latex to prevent coagulation during transportation and storage (see RUBBER COMPOUNDING). (8) In the food and beverage industry as a source of nitrogen required for the growth of yeast and microorganisms and also to control pH in yeast production; as ammoniating agent for glycyrrhizin; as an extractant for bitter principles; and as a source of nitrogen for ruminant feeding when properly combined with molasses (see FEEDS AND FEED ADDITIVES; FERMENTATION; FOODS). (9) As a curing agent in making leather, and as a slime and mold preventative in tanning liquors (see LEATHER), in the manufacture of mothproofing and other protective agents for furs and hides. (10) In the manufacture of pharmaceuticals, such as sulfanilamide, sulfathiazole, sulfapyridine, and other sulfur drugs (see ANTIBACTERIAL AGENTS, SYNTHETIC; PHARMACEUTICALS); vitamins (qv), antimalarials, methionine and other amino acids (qv); and of dentifrices (qv), lotions, and cosmetics (qv). (11) In the manufacture of household ammonia, detergents, and cleansers. (12) In combination with chlorine to purify industrial and municipal water supplies; and as an oxygen scavenger in treating boiler feedwater. (13) In the manufacture of numerous organic and inorganic chemicals, such as cyanides, amides, amines, nitrites, and dye intermediates. (14) As a precipitant in uranium concentrate production.

By-product Ammonia

Recovering ammonia as a by-product from other processes accounted for less than 1% of the total U.S. ammonia production in 1987. The principal source of by-product ammonia is from the coking of coal. In the coking operation, about 15–20% of the nitrogen present in the coal is liberated as ammonia and is recovered from the coke oven gas as ammonium sulfate, ammonia liquor, and ammonium phosphates. The recovery product depends on the scrubbing medium employed, sulfuric acid, milk of lime, and phosphoric acid, respectively. Ammonium sulfate recovery by the so-called semidirect process, is most widely employed.

In the semidirect process, (Fig. 23) the raw coke oven gas is cooled to condense tar and ammonia liquor. The heavy layer, tar phase, is pumped to storage and the aqueous layer containing free and fixed ammonia is subsequently processed in a still operation. Free ammonia is that which is in a form which readily dissociates by heat. Fixed ammonia is in a form which requires the presence of an alkali, such as milk of lime, to effect the ammonia release.

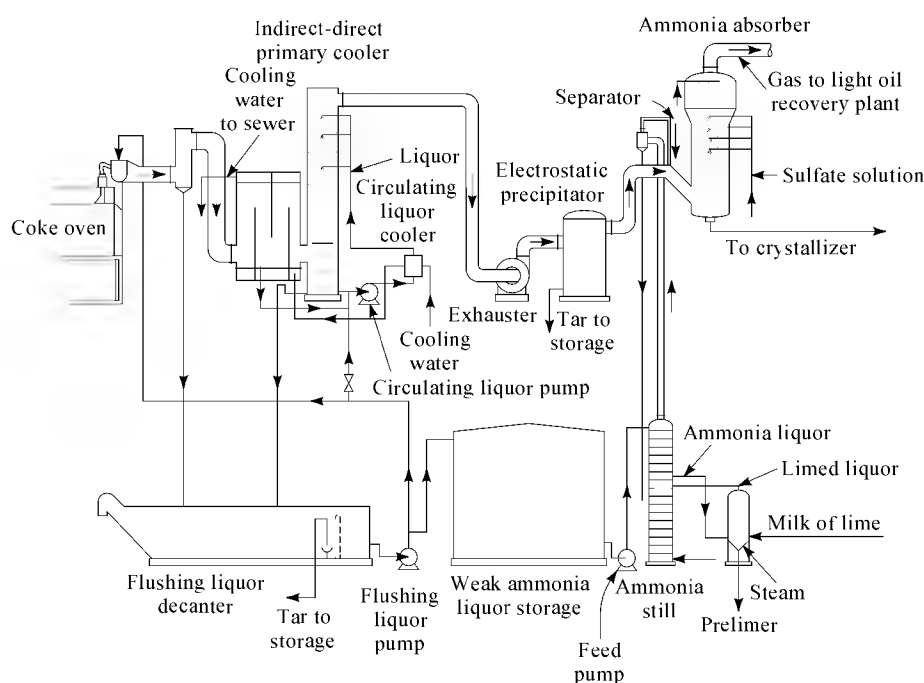
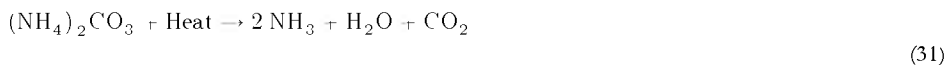
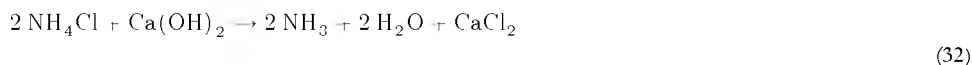


Fig. 23. Semidirect process for recovery of by-product ammonium sulfate.

Ammonia liquor is fed to the top of the still and heated using steam vapor which dissociates the unstable ammonium salts, eg, ammonium carbonate and ammonium sulfite.



The liquor is then treated with calcium hydroxide (milk of lime) which reacts with the fixed salts, mostly ammonium chloride, to liberate ammonia. The liquor is regenerated in a steam stripping operation.



The gaseous ammonia is passed through electrostatic precipitators for particulate removal and mixed with the cooled gas stream. The combined stream flows to the ammonia absorber where the ammonia is recovered by reaction with a dilute solution of sulfuric acid to form ammonium sulfate. Ammonium sulfate precipitates as small crystals after the solution becomes saturated and is withdrawn as a slurry. The slurry is further processed in centrifuge facilities for recovery. Crystal size can be increased by employing one of two processes (99), either low differential controlled crystallization or mechanical size enlargement by continuous compacting and granulation.

Chevron's WWT (wastewater treatment) process treats refinery sour water for reuse, producing ammonia and hydrogen sulfide [7783-06-04] as by-products (100). Degassed sour water is fed to the first of two strippers. Here hydrogen sulfide is stripped overhead while water and ammonia flow out the column bottoms. The bottoms from the first stripper is fed to the second stripper which produces ammonia as the overhead product. The gaseous ammonia is next treated for hydrogen sulfide and water removal, compressed, and further purified. Ammonia recovery options include anhydrous liquid ammonia, aqueous liquid ammonia, and ammonia vapor for incineration. There are more than 20 reported units in operation, the annual production of ammonia from this process is about 200,000 t.

Nonconventional Sources of Ammonia

The search for a high yield alternative energy route to ammonia, in an effort to meet fertilizer demands and conserve natural gas reserves, is a continuing one. Energy sources such as photochemical, microwave, magnetohydrodynamic, and chemo-nuclear are being explored in the laboratory for fixing nitrogen as ammonia. The economic viability of these processes depends on the ability to scale-up to large capacities, to increase low yields, and to incorporate efficient energy recovery mechanisms.

A novel route to ammonia synthesis using methane, but without first producing hydrogen, has been proposed (101).



A ruthenium-based catalyst is used but low yields resulting from unexpected side reactions are still a problem. Refinement of alternative route ammonia manufacture and advances in genetic engineering, allowing a wider range of plant life to fix nitrogen *in situ*, should provide assurance for long term world food needs.

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AMMONIUM COMPOUNDS

There are a considerable number of stable crystalline salts of the ammonium ion [14798-03-9], NH₄⁺. Several are of commercial importance because of large scale consumption in fertilizer and industrial markets. The ammonium ion is about the same size as the potassium and rubidium ions, so these salts are often isomorphous and have similar solubility in water. Compounds in which the ammonium ion is combined with a large, uninegative anion are usually the most stable. Ammonium salts containing a small, highly charged anion generally dissociate easily into ammonia (qv) and the free acid (1). At about 300°C most simple ammonium salts volatilize with dissociation, for example



Exceptions are salts of oxidizing anions, which decompose with oxidation of the ammonium ion to nitrous oxide [10024-97-2], N₂O, or nitrogen, N₂.

A number of simple, standard methods have been developed for the analysis of ammonium compounds, several of which have been adapted to automated or instrumental methods. Ammonium content is most easily determined by adding excess sodium hydroxide to a solution of the salt. Liberated ammonia is then distilled into standard sulfuric acid and the excess acid titrated. Other methods include colorimetry (2) and the use of a specific ion electrode (3).

Covered elsewhere are: ammonium bifluoride [1341-49-7], NH₄HF₂, and ammonium fluoride [12125-01-8] NH₄F, (see FLUORINE COMPOUNDS); ammonium borates [12007-89-5]/NH₄B₅O₈, (see BORON COMPOUNDS); ammonium chromate [7788-98-9], NH₄Cr₂O₄, and ammonium dichromate [7789-09-5], NH₄Cr₂O₇, (see CHROMIUM COMPOUNDS); ammonium cyanide [12211-52-8], NH₄CN, (see CYANIDES); ammonium glutamate [20806-32-0], NH₄C₅H₈NO₄, (see AMINO ACIDS); ammonium hydroxide [1336-21-6], NH₄OH, (see AMMONIA); ammonium molybdate [13106-76-8], (NH₄)₂MoO₄, (see MOLYBDENUM COMPOUNDS); ammonium oxalate [1113-38-8], (NH₄)₂C₂O₄, (see OXALIC ACID); ammonium phosphate dibasic [7783-28-0], (NH₄)₂HPO₄, and ammonium phosphate monobasic [7722-76-1], (NH₄)H₂PO₄, (see PHOSPHORIC ACID AND THE PHOSPHATES); ammonium sulfamate [7773-06-0], NH₄SO₃NH₂, (see SULFAMIC ACID AND SULFAMATES); and ammonium thiosulfate [7783-18-8], (NH₄)₂S₂O₃ (see THIOSULFATES).

Ammonium Acetates

Both normal or neutral ammonium acetate [631-61-8], NH₄C₂H₃O₂, and the acid salt are known. The normal salt results from exact neutralization of acetic acid using ammonia; the acid salt is composed of the neutral salt and acetic acid.

The normal salt, CH₃COONH₄, is a white, deliquescent, crystalline solid, formula wt 77.08, having a specific gravity of 1.073. It is quite soluble in water or ethanol: 148 g dissolve in 100 g of water at 4°C. The salt's solubility in water increases only slightly as temperature increases up to about 25°C. The specific gravity of aqueous neutral ammonium acetate ranges from 1.022 to 1.092 as solution concentration increases from 10 to 50 wt % (4). The normal salt melts at 114°C, but decomposes before reaching its boiling point.

Ammonium acetate solutions formed by neutralizing acetic acid using ammonium hydroxide are essentially neutral. Thus, these solutions are suitable for standardization of electrodes, and for use as titration standards. Solutions must be used while fresh, however, as they become acidic on standing.

Isolation of dry, normal ammonium acetate, prepared by neutralizing acetic acid with anhydrous ammonia or ammonium carbonate, is difficult because of ammonia loss during evaporation of water. Consequently, commercial grades of ammonium acetate are often mixtures of the neutral and acid salts, or are supplied as ammonium acetate solution [8013-61-4].

The acidic double salt of ammonium acetate and acetic acid [25007-86-7], CH₃COONH₄·CH₃COOH, is made by dissolving the neutral salt in hot acetic acid or by distilling the neutral salt. During distillation the acid salt is formed as a heavy oil that solidifies on cooling. It crystallizes as long, deliquescent needles that melt at 66°C. Acid ammonium acetate is readily soluble in both water and alcohol.

Ammonium acetate has limited commercial uses. It serves as an analytical reagent, and in the production of foam rubber and vinyl plastics; it is also used as a diaphoretic and diuretic in pharmaceutical applications. The salt has some importance as a mordant in textile dyeing. In a hot dye bath, gradual volatilization of ammonia from the ammonium acetate causes the dye solution to become progressively more acidic. This increase in acidity enhances the color and permanence of the dyeing process.

Ammonium Carbonates

The earliest mention of an ammonium carbonate, salt of hartshorn, appears in English manuscripts of the 14th century. As the name implies, the material was obtained by dry distillation of animal waste such as horn, leather, and hooves. Although many salts have been described in the literature for the ternary NH₃–CO₂–H₂O system, most, except for ammonium bicarbonate [1066-33-7], NH₄HCO₃, ammonium carbonate [506-87-6], (NH₄)₂CO₃, and ammonium carbamate [1111-78-0], NH₄CO₂NH₂, are mixtures (5,6).

AMMONIUM BICARBONATE

Ammonium bicarbonate, also known as ammonium hydrogen carbonate or ammonium acid carbonate, is easily formed. However, it decomposes below its melting point, dissociating into ammonia, carbon dioxide, and water. If this process is carefully controlled, these compounds condense to reform ammonium bicarbonate. The vapor pressures of dry ammonium bicarbonate are shown below (7). (To convert kPa to mm Hg, multiply by 7.5.)

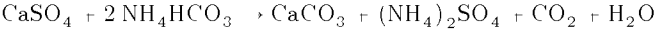
<i>Temperature, °C</i>	<i>Vapor Pressure, kPa</i>	<i>Temperature °C</i>	<i>Vapor Pressure, kPa</i>
25.4	7.85	50.0	52.65
34.2	16.26	55.8	82.11
40.7	26.79	59.3	108.64
45.0	37.06		

Ammonium bicarbonate, sp gr 1.586, formula wt 79.06, is the only compound in the NH₃–CO₂–H₂O system that dissolves in water without decomposition. Solubility in 100 g of H₂O ranges from 11.9 g at 0°C to 59.2 g 100 g of H₂O at 60°C (8). The heat of formation from gaseous ammonia and carbon dioxide and liquid water is 126.5 kJ/mol (30.2 kcal/mol). Ammonium bicarbonate is manufactured by passing carbon dioxide gas

countercurrently through a descending stream of aqua ammonia. The reaction is normally carried out in a packed tower or absorption column. Because the reaction is exothermic, cooling the lower portion of the tower is advisable. Concentration of the solution is monitored by determining specific gravity. When the solution is sufficiently saturated, crystallization of ammonium bicarbonate occurs. The crystals are separated from the mother liquor by filtration or centrifugation and washing, and are dried using 50°C air.

Ammonium bicarbonate is produced as both food and standard grade and the available products are normally very pure. Although purification is possible by sublimation at low temperatures, it is more economical to prepare the desired product directly by using ammonia and carbon dioxide of high purity.

When heated, ammonium bicarbonate decomposes to ammonia, water, and carbon dioxide, leaving no solid residue. This property explains its use as a leavening agent for certain baked goods (see BAKERY PROCESSES AND LEAVENING AGENTS). At about 150°C, 1 kg yields 1.3 m³ (46.2 ft³) of STP gas. Ammonium bicarbonate is also used in pharmaceuticals (qv), in production of ammonium salts, and in formulation of fire-extinguishing agents (qv). It is effective in scale removal, for example, in heat-exchanger tubes by dissolving thin layers of calcium sulfate.



For thicker layers of scale, alternate treatments using dilute hydrochloric acid appear desirable (9). The price of ammonium bicarbonate in June 1991 was about \$0.72/kg; its DOT number is NA9081.

AMMONIUM CARBONATE

Normal ammonium carbonate, mp 43°C, formula wt 96.09, is a crystalline solid. The commercial product may be produced by passing carbon dioxide into an absorption column containing aqueous ammonia solution and causing distillation. Vapors containing ammonia, carbon dioxide, and water condense to give a solid mass of crystals. Ammonium carbonate is the principal ingredient of smelling salts because of its characteristic strong ammonia odor. It is also used for other medicinal purposes and as a leavening agent.

Ammonium Citrate

Diammonium citrate [3012-65-5], (NH₄)₂C₆H₅O₇, mol wt 226.19, is soluble in an equal weight of water, but is only slightly soluble in ethanol. The pH of a 0.1 M solution is 4.3. It is made by neutralization of citric acid with ammonia; the crystalline or granular product is used as a chemical reagent and pharmaceutically as a diuretic. The price of ammonium citrate in June 1991 was \$8.16/kg in drums.

Ammonium Halides

Ammonium chloride [12125-02-9], NH₄Cl, ammonium bromide [12124-97-9], NH₄Br, and ammonium iodide [12027-06-4], NH₄I, are crystalline, ionic compounds of formula wts 53.49, 97.94, and 144.94, respectively. Their densities d₄²⁰ systematically follow the increase in formula weight: 1.53, 2.40, and 2.52. All three exist in two crystal modifications (10): the chloride, bromide, and iodide have the CsCl structure below temperatures of 184.5, 137.8, and 17.6°C, respectively; each reversibly transforms to the NaCl structure at higher temperatures.

The solubility of the ammonium halides in water also increases with increasing formula weight. For ammonium chloride, the integral heat of solution to saturation is 15.7 kJ/mol (3.75 kcal/mol); at saturation, the differential heat of solution is 15.2 kJ/mol (3.63 kcal/mol). The solubility of all three salts is given in Table 1 (7).

Table 1. Solubilities of Ammonium Halides

Temperature, °C	Solubility, g/100 g water			Temperature, °C	Solubility, g/100 g water		
	NH ₄ Cl	NH ₄ Br	NH ₄ I		NH ₄ Cl	NH ₄ Br	NH ₄ I
0	29.4	60.6	154.2	60	55.3	107.8	208.9
20	37.2	75.5	172.3	80	65.6	126.0	228.8
40	45.8	91.1	190.5	100	77.3	145.6	250.3

All ammonium halides exhibit high vapor pressures at elevated temperatures, and thus, sublime readily. The vapor formed on sublimation consists not of discrete ammonium halide molecules, but is composed primarily of equal volumes of ammonia and hydrogen halide. The vapor densities are essentially half that expected for the vaporous ammonium halides. Vapor pressures at various temperatures are given in Table 2 (11). Latent heats of sublimation, assuming complete dissociation of vapors and including heats of dissociation are 165.7, 184.1, and 176.6 kJ/mol (39.6, 44.0, and 42.2 kcal/mol), for NH₄Cl, NH₄Br, and NH₄I, respectively.

Table 2. Vapor Pressures of Ammonium Halides

Temperature, °C	Vapor pressure, kPa ^a		
	NH ₄ Cl	NH ₄ Br	NH ₄ I
250	6.5		
280	17.9		
300	33.5	7.3	
320	60.9	13.3	
338	101.1		
360		41.2	31.3
380		73.4	54.1
395		101.1	
400		115.4	89.8
405			101.1

^a To convert kPa to mm Hg, multiply by 7.5.

The heat of formation of ammonium chloride from the elements is 317 kJ/mol (75.8 kcal/mol); it is 175 kJ/mol (41.9 kcal/mol) from gaseous ammonia and gaseous hydrogen chloride. The heat of formation of ammonium bromide from the elements, bromine in the liquid form, is 273 kJ/mol (65.3 kcal/mol); for ammonium iodide, the corresponding heat of formation is 206 kJ/mol (49.3 kcal/mol). Iodine is in the solid state.

Aqueous solutions of ammonium halides, like the other ammonium salts of strong acids, are acidic; on storage and exposure these solutions tend to become more acidic through ammonia loss. They also have a pronounced tendency to attack ferrous and other metal surfaces, especially those of copper and copper alloys.

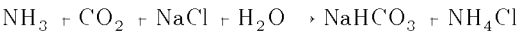
AMMONIUM CHLORIDE

Manufacture. The history of ammonium chloride manufacture is linked to the birth of the soda and synthetic ammonia industries. Consequently this halide has always been a by-product in great supply. Production by direct reaction of ammonia and hydrochloric acid is simple but usually economically unattractive; a process based on metathesis or double decomposition is generally preferred.

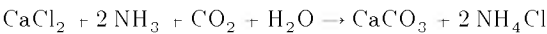
Several commercial grades are available: fine crystals of 99 to 100° purity, large crystals, pressed lumps, rods, and granular material.

Double-Decomposition Methods. Double-decomposition processes all involve the reaction of sodium chloride, the cheapest chlorine source, with an ammonium salt. The latter may be supplied directly, or generated *in situ* by the reaction of ammonia and a supplementary ingredient. Ammonium chloride and a sodium salt are formed. The sodium salt is typically less soluble and is separated at higher temperatures; ammonium chloride is recovered from the filtrate by cooling.

Ammonia-Soda Process. Ammonium chloride is made as a by-product of the classic Solvay process , used to manufacture sodium carbonate (12,13) (see ALKALI AND CHLORINE PRODUCTS, SODIUM CARBONATE). The method involves reaction of ammonia, carbon dioxide, and sodium chloride in water

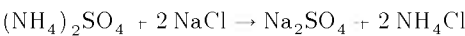


Sodium bicarbonate precipitates from solution and is recovered by filtration. Ammonium chloride is then crystallized from the filtrate, separated, washed, and dried. The exact proportion of ammonium chloride recovered depends on the relative demands for sodium carbonate and ammonium chloride. If economic conditions require, part of the ammonia can be recovered and returned to the brine-ammoniation step by distillation of the ammonium chloride solution in the presence of lime. The spent calcium chloride liquor, a final product in manufacture of sodium carbonate by the ammonia–soda process, can also be used to obtain ammonium chloride. This liquor is treated with ammonia and carbon dioxide



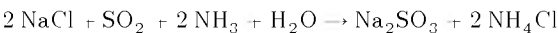
Calcium carbonate is removed by filtration leaving an ammonium chloride solution.

Ammonium Sulfate–Sodium Chloride Process. Ammonium sulfate, a readily available by-product, has been much used to make ammonium chloride by a double decomposition reaction with sodium chloride.



The ammonium sulfate and sodium chloride are simultaneously dissolved, preferably in a heel of ammonium chloride solution. The sodium chloride is typically in excess of about 5° . The pasty mixture is kept hot and agitated vigorously. When the mixture is separated by vacuum filtration, the filter and all connections are heated to avoid crust formation. The crystalline sodium sulfate is washed to remove essentially all of the ammonium chloride and the washings recycled to the process. The ammonium chloride filtrate is transferred to acid resistant crystallizing pans, concentrated, and cooled to effect crystallization. The crystalline NH₄Cl is washed with water to remove sulfate and dried to yield a product of high purity. No attempt is made to recover ammonium chloride remaining in solution. The mother liquor remaining after crystallization is reused as a heel.

Ammonium Sulfite–Sodium Chloride Process. Ammonium chloride has been produced by the reaction of ammonium sulfite [10196-04-0], NH₄SO₃, and sodium chloride in a large Canadian plant (14). Ammonium sulfite is never actually isolated, rather ammonia and sulfur dioxide react in water with sodium chloride.



This process is only practical when the raw materials are readily available and of high purity.

The sodium sulfite precipitates first and is removed by centrifugation, washed with water, and dried. The mother liquor containing ammonium chloride is sent to crystallizing tanks and the salt thus formed is washed and dried, giving a product said to analyze well over 99° .

Direct Neutralization. Because of the availability of by-product ammonium salts, the double decomposition routes are usually more favorable economically for ammonium chloride manufacture. However, where surplus hydrogen chloride is available, the direct neutralization process has been used (15)



The reaction is very exothermic and the heat generated is used to evaporate a large part of the water present when aqueous hydrochloric acid is used. Batch or continuous crystallization is then employed to recover the ammonium chloride.

A Brazilian company has reportedly produced ammonium chloride from hydrogen chloride gas (16). Hydrogen chloride is mixed with air and introduced into a saturated ammonium chloride suspension at 80 °C. Excess ammonia is added to a conical section of the saturator to maintain a pH of 8. The ammonium chloride is recovered from the suspension by thickening in a hydroclone, followed by centrifugation and drying. Mother liquor and the water used to scrub waste gases, are returned to the saturator.

Economic Aspects and Uses. Ammonium chloride is used as a nitrogen source for fertilization of rice, wheat, and other crops in Japan, China, India, and Southeast Asia. Japan is a large producer, much of which is as by-product.

Ammonium chloride has a number of industrial uses, most importantly in the manufacture of dry-cell batteries , where it serves as an electrolyte. It is also used to make quarrying explosives, as a hardener for formaldehyde-based adhesives, as a flame suppressant , and in etching solutions in the manufacture of printed circuit boards. Other applications include use as a component of fluxes in zinc and tin plating, and for electrolytic refining of zinc.

Technical grade ammonium chloride is widely available as the crystalline salt; technical rods and granules are also available. In June 1991, the price of the technical salt was quoted as \$0.43 /kg. Its DOT number is NA9085.

AMMONIUM BROMIDE AND IODIDE

Manufacture. Ammonium bromide and Ammonium iodide are manufactured either by the reaction of ammonia with the corresponding hydrohalic acid or, more economically, by the reaction of ammonia with elemental bromine or iodine. In the latter reaction, an excess of ammonia must be used.



For ammonium bromide, another method involving reaction of an aqueous bromine solution and iron filings has been used. The solution of ferrous and ferric bromide thus formed then reacts with ammonia to precipitate hydrated oxides of iron. Ammonium bromide can be recovered by crystallization from the concentrated liquor.

Economic Aspects and Uses. Ammonium bromide is available as a dry technical grade or as 38 to 45° solutions. It is used to manufacture chemical intermediates, and in photographic chemicals; it also has some flame retardant applications. In June 1991, its price was quoted as \$2.66 /kg.

Ammonium iodide has limited use in photographic and pharmaceutical preparations.

Ammonium Nitrate

Ammonium nitrate [6484-52-2], NH₄NO₃, formula wt 80.04, is the most commercially important ammonium compound both in terms of production volume and usage. It is the principal component of most industrial explosives and nonmilitary blasting compositions; however, it is used primarily as a nitrogen fertilizer. Ammonium nitrate does not occur in nature because it is very soluble. It was first described in 1659 by the German scientist Glauber, who prepared it by reaction of ammonium carbonate and nitric acid. He called it nitrium flammans because its yellow flame (from traces of sodium) was

different from that of potassium nitrate.

Ammonium nitrate fertilizer incorporates nitrogen in both of the forms taken up by crops: ammonia and nitrate ion. Fertilizers (qv) containing only ammoniacal nitrogen are often less effective, as many important crops tend to take up nitrogen mainly in the nitrate form and the ammonium ions must be transformed into nitrate by soil organisms before the nitrogen is readily available. This transformation is slow in cool, temperate zone soils. Thus, ammonium nitrate is a preferred source of fertilizer nitrogen in some countries.

One general disadvantage of nitrogen fertilizers, and ammonium nitrate in particular, is that the nitrate ion is more prone to leach through the soil profile and enter the groundwater. The presence of nitrate in groundwater became an important environmental issue in the 1980s (see GROUNDWATER MONITORING). Efforts by farmers to address this problem have focused on improved management techniques, such as multiple or delayed applications, accurate and efficient placement, and the use of cover crops to take up residual nitrogen and reduce erosion. Controlling the dissolution and release of ammonium nitrate into the soil by use of rosin-coated fertilizer (17) has also been suggested.

Physical and Chemical Properties. Ammonium nitrate is a white, crystalline salt, d_4^{20} 1.725, that is highly soluble in water, as shown in Table 3 (7). Although it is very hygroscopic, it does not form hydrates. This hygroscopic nature complicates its usage in explosives, and until about 1940, was a serious impediment to its extensive use in fertilizers. The solid salt picks up water from air when the vapor pressure of water exceeds the vapor pressure of a saturated aqueous ammonium nitrate solution (see Table 4).

Table 3. Solubility of Ammonium Nitrate

Solubility of NH ₄ NO ₃ , g/100 g			Solubility of NH ₄ NO ₃ , g/100 g		
Temperature, °C	Water	Soln	Temperature, °C	Water	Soln
0	118	54.2	60	410	80.4
10	150	60.0	70	499	83.3
20	187	65.2	80	576	85.2
30	232	69.9	90	740	88.1
40	297	74.8	100	843	89.4
50	346	77.6			

Table 4. Vapor Pressure of Ammonium Nitrate Solutions

Temperature, °C	Vapor pressure, kPa ^a	
	Water	Saturated NH ₄ NO ₃ soln
10	1.2	0.85
20	2.3	1.5
30	4.2	2.5
40	7.4	3.9

^a To convert kPa to mm Hg, multiply by 7.5.

The boiling point of ammonium nitrate–water solutions, given in Table 5, indicates the temperatures required for removing water (18).

Table 5. Boiling Point of Ammonium Nitrate Solutions

NH ₄ NO ₃ , wt %	Bp, °C	NH ₄ NO ₃ , wt %	Bp, °C	NH ₄ NO ₃ , wt %	Bp, °C
10	101	60	113.5	94	165
20	102.5	70	119.5	95	170
30	104	80	128.5	96	182
40	107.5	85	136	98	203
50	109.5	90	157	99	222

Solid ammonium nitrate occurs in five different crystalline forms (19) (Table 6) detectable by time–temperature cooling curves. Because all phase changes involve either shrinkage or expansion of the crystals, there can be a considerable effect on the physical condition of the solid material. This is particularly true of the 32.3°C transition point which is so close to normal storage temperature during hot weather.

Table 6. Crystalline Forms of Ammonium Nitrate

Designation	Temperature range, °C	Crystal system
α	< 18	tetragonal
β	18–32.1	rhombic
γ	32.1–84.2	rhombic
δ	84.2–125.2	tetragonal
ε	125.2–169.6	cubic

The specific heat of solid β-phase ammonium nitrate is 1.70 J/g (0.406 cal/g) between 0 and 31°C; the specific heats of aqueous NH₄NO₃ solutions are shown in Table 7 (8,20). The coefficient of expansion is 0.000920 at 0°C, 0.000982 at 20°C, and 0.001113 at 100°C; the heat of formation from the elements is 364 kJ/mol (87.1 kcal/mol).

Table 7. Specific Heats of Aqueous Solutions of Ammonium Nitrate at 100°C

NH ₄ NO ₃ , wt %	Specific heat, J/g ^a	NH ₄ NO ₃ , wt %	Specific heat, J/g
10	3.9	70	2.4
30	3.4	90	1.9
50	2.9		

^a To convert J to cal, divide by 4.184.

Ammonium nitrate has a negative heat of solution in water, and can therefore be used to prepare freezing mixtures. Dissolution of ammonium nitrate in anhydrous ammonia, however, is accompanied by heat evolution. In dilute solution the heat of neutralization of nitric acid using ammonia is 51.8 kJ mol (12.4 kcal mo).

Decomposition and Detonation Hazard. Ammonium nitrate is considered a very stable salt, even though ammonium salts of strong acids generally lose ammonia and become slightly acidic on storage. For ammonium nitrate, endothermic dissociation from lowering pH occurs above 169°C.



When the salt is heated to temperatures from 200 to 230°C, exothermic decomposition occurs (4,21). The reaction is rapid, but it can be controlled, and it is the basis for the commercial preparation of nitrous oxide [10024-97-2].



Above 230°C, exothermic elimination of N₂ and NO₂ begin.



The final violent exothermic reaction occurs with great rapidity when ammonium nitrate detonates.



Ammonium nitrate is normally classified as an oxidizing agent. The pure salt is not classed as an explosive because it is difficult to detonate. Spark, flame, or friction do not cause detonation, and ammonium nitrate is relatively insensitive to shock. However, a variety of substances, such as chloride and oil, are known to sensitize the material, so manufacturers strive to eliminate such substances from their processes.

When used in blasting, ammonium nitrate is mixed with fuel oil and sometimes sensitizers such as powdered aluminum. Lower density ammonium nitrate is preferred for explosive formulation, because it absorbs the oil more effectively. When detonated, these mixtures have an explosive power of 40 to 50% that of TNT (see EXPLOSIVES AND PROPELLANTS).

Manufacture. Historically, ammonium nitrate was manufactured by a double decomposition method using sodium nitrate and either ammonium sulfate or ammonium chloride. Modern commercial processes, however, rely almost exclusively on the neutralization of nitric acid (qv), produced from ammonia through catalyzed oxidation, with ammonia. Manufacturers commonly use onsite ammonia although some ammonium nitrate is made from purchased ammonia. Solid product used as fertilizer has been the predominant form produced. However, sale of ammonium nitrate as a component in urea–ammonium nitrate liquid fertilizer has grown to where about half the ammonium nitrate produced is actually marketed as a solution.

Three steps are essential to ammonium nitrate manufacture: neutralization of nitric acid with ammonia to produce a concentrated solution; evaporation to give a melt; and processing by prilling or granulation to give the commercial solid product.

Neutralization. The reaction of ammonia and nitric acid is highly exothermic and the heat released evaporates water, most commonly concentrating the reaction mixture to 83–87% ammonium nitrate. Both reactants are also volatile at the resulting temperatures, thus close control of reactor conditions is necessary to prevent loss of material. Strict temperature regulation in the entire reactor, normally achieved by regulating the addition of feeds and by removal of heat, is particularly important. The heat removed can be recovered for acid preheating, ammonia evaporation, or evaporation of additional water. To avoid localized overheating, reactors are also designed for excellent mixing and utilize automatic pH control.

Neutralizers can be of three designs, depending on the temperature in the reactor zone. They may operate under, exactly at, or above the atmospheric boiling point of the contained ammonium nitrate solution.

Vacuum flash processes, which operate under the atmospheric boiling point of the solution, include the Uhde–I.G. Farbenindustrie process and the closely related Kestner process (22). In these, ammonia, nitric acid, and recirculated ammonium nitrate solution are fed into the neutralizer. Hot solution overflows to an intermediate tank and then to a flash evaporator kept at 18–20 kPa (0.18–0.2 atm) absolute pressure. Partial evaporation of water at this point cools and concentrates the solution, part of which is routed to evaporation. The rest is circulated to the neutralizer.

The ICI process is an example of neutralization at atmospheric pressure. Nitric acid feed is preheated by part of the vapors produced in the neutralizer and is then split into two streams. Recycled, undersized product is dissolved in one stream, conditioning material in the other. The recombined streams are added to a two stage neutralizer along with ammonia and recirculated solution to give 87 to 89% ammonium nitrate feed for evaporation. The C&I–Girdler–Cominco process is similar in principle; the Pintsch-Bamag (23) process uses a two-stage neutralizer without recirculation.

The Fauser process (24), which operates above atmospheric pressure, was an early attempt to fully utilize the heat of neutralization. The neutralizing zone of the enclosed reactor operates at 500–600 kPa (5 to 6 atm). Reactants enter at the bottom of this chamber and hot ammonium nitrate streams upward, where it is discharged continuously into an outer vessel operated at atmospheric pressure. The arriving solution loses part of its water; subsequently most is recirculated through the outer vessel to the lower neutralizing space, while part is removed for further processing. Ammonia and nitric acid feed streams are preheated by partial utilization of the steam from the outer vessel. Variations of the Fauser process are used extensively in the USSR; among these are the ITR, GIAP-Kemerova, and TGL processes.

The Stamicarbon (22) and Kaltenbach high concentration processes are designed to use the evaporated water vapor produced by pressure neutralization to heat the evaporator used for concentration. The Kaltenbach neutralizer operates at 350 kPa (3.5 bar) and 175°C, and produces steam used to concentrate the solution to 95% in a vacuum evaporator. A recent variation uses a final atmospheric evaporator to produce a 99.7% melt (22).

Other processes, including the Soci  t   Belge de l'Azote and Union Chimique Belge (22) are designed to achieve even higher heat recovery which is inherently possible through use of pressure neutralization.

Concentration. Evaporation procedures depend on the concentration of the solution produced during neutralization and the water content required for the subsequent production of solid product. Neutralizer solutions can contain as little as 2% and as much as 25% water; feeds to drum granulators can contain 5% water, prill towers 0.3 to 0.5% water.

Since about 1965, efficient vacuum evaporators have been used in most plants. Second stage evaporators, where the ammonium nitrate is concentrated to more than 99%, are designed to retain only a small volume of melt, have short residence times, and are protected from overheating and contamination by sensitizers. Falling film units are especially suited for this application.

Solid Finished Product. The final step in ammonium nitrate fertilizer manufacture is the production of a uniformly sized, abrasion and crush-resistant, and free-flowing solid possessing good storage properties. Besides being hygroscopic, ammonium nitrate is subject to degradation, or "sugaring", which occurs during storage as temperatures fluctuate across the 32.1°C crystal phase change. Most manufacturers seek to overcome this latter problem by adding a stabilizing agent to the melt. These additives include magnesium nitrate, Mississippi Chemical Corporation's Permalene-34, and C&I–Girdler's NUCLO-ADD.

Graining, flaking, and spraying have all been used to make solid ammonium nitrate particles. Most plants have adopted various prilling or granulation processes. Crystallized ammonium nitrate has been produced occasionally in small quantities for use in specialty explosives. The Tennessee Valley Authority developed and operated a vacuum crystallization process (25), but the comparatively small crystals were not well received as a fertilizer. The process was subsequently modified to pan granulation (26).

Prilling Process. Prilling is the formation of a rounded, granular solid by allowing molten droplets to fall through a fluid cooling medium. Prilling of ammonium nitrate involves spraying the concentrated (96% or 99+%) solution into the top of a large tower. The descending droplets are cooled by an upward flow of air, solidifying into spherical prills that are collected at the bottom. The process yields particles that vary in size depending on the residual

moisture of solution, air temperature, and flow rate.

The 96–97° ammonium nitrate solutions are sprayed into towers 33 to 60 m high to produce low density 770 kg m³ (48 lbs ft³) prills favored for use in ammonium nitrate–fuel oil blasting agents. A drying step is required after prilling. This porous product promotes propagation of detonation and allows for a higher fuel oil loading.

The 99.7–99.8° solutions are sprayed into towers only 20 to 30 m high (27) to give high density 860 kg m³ (54 lbs ft³) prills preferred by the fertilizer industry. These prills, which require cooling but no drying, are sometimes coated using 2.5–3° of activated clay or diatomaceous earth, although some producers add chemical additives to the melt, giving a product needing no surface conditioner.

Granulation Processes. In the early 1970s, production of large-particle ammonium nitrate using the spheroidizer granulation process was adopted by several manufacturers. This process, developed by Cominco, Ltd. (Canada) and the C & I–Girdler Corporation, is an adaptation of one used for production of other fertilizers (28). Ammonium nitrate is layered in onion-skin fashion on small seed particles by spraying a 99 ± % solution on a dense cascading curtain of granules. This process is carried out in a 3.5–4.5 m diameter by 14–18 m rotating drum having specially designed flights.

The well-rounded particles produced are screened and cooled, giving granules having a moisture content of about 0.1°; they do not require a conditioner. These granules also have a higher crushing strength than prills, and are less subject to breakdown in storage and handling. The process is used by several ammonium nitrate producers in the United States; most calcium ammonium nitrate [39368-85-9] and ammonium nitrate sulfate [12436-94-1] producers outside of the United States also use this granulation technique.

A fluid bed granulation process developed by Nederlandse Stikstof Maatschappij (NSM) is also available (29). The granules grow from single seed particles. These are fed to a baffled, rectangular vessel, where they are fluidized by a flow of preheated air. A 97° ammonium nitrate solution is sprayed upward into this bed of particles, continuously coating them. Efficient air contact during the 15 min residence time allows evaporation of water as the particles grow in size. The largest granules finally settle and flow from the bottom of the vessel. Pollution control is effected by a wet scrubber and presents few problems.

Blungers and classic drum granulator equipment have also been adapted to the production of granular ammonium nitrate. In the Norsk Hydro Fertilizer, Ltd. process a 92–95° solution is sprayed onto a bed of recycled fines inside a drum granulator (30). Granulator temperatures are held between 85 and 100°C; a small amount of ammonia is also fed to the rolling bed. Material discharged from the granulator is dried either by indirectly heated air or by a gas-fired burner.

Granulation processes offer a number of important advantages. The most significant are decreased pollution problems and the ability to produce granules of almost any reasonable size allowing close size matching with granular ammonium phosphates and potassium chloride in the preparation of NPK fertilizers (26).

Quality of Product. Ammonium nitrate, commonly made from pure synthetic raw materials, is itself of high purity. If the product is intended for use in explosives, it should be at least 99° ammonium nitrate and contain no more than 0.15° water. It should contain only small amounts of water-insoluble and ether-soluble material, sulfates and chlorides, and should not contain nitrites. The solid product ought to be free from alkalinity, but be only slightly acidic.

If the product is to be used in the manufacture of nitrous oxide, an anesthetic gas, a purity of not less than 99.5° is required. The salt must be almost completely free of contaminating organic matter, iron, sulfate, and chloride.

Safety Considerations. Ammonium nitrate can be considered a safe material if treated and handled properly. Potential hazards include those associated with fire, decomposition accompanied by generation of toxic fumes, and explosion.

Although ammonium nitrate does not itself burn, it is a strong oxidizer capable of supporting the combustion of numerous substances when heated. It can support and intensify a fire even when air is excluded. Fires involving ammonium nitrate also present a toxic hazard from the release of nitrogen oxides, even though the solid itself is generally considered not to be toxic.

Pure ammonium nitrate is a relatively insensitive explosive material, requiring high initiation energy, but when detonated it can have about 70° of the disruptive strength of nitroglycerine. In 1947, after vigorous fires, two explosions occurred on freighters loaded with heavy paper containers of fertilizer grade ammonium nitrate. These explosions resulted in the proposal of precautions for the handling and transportation of ammonium nitrate (31). Thus, ammonium nitrate must be considered a high explosive under the following three conditions: bolstering by a high velocity explosive, confinement at elevated temperatures, and presence of oxidizable materials.

Economic Aspects and Uses. Before World War II most ammonium nitrate was used as an ingredient in high explosives. Subsequently its use as a fertilizer grew rapidly, absorbing about 90° of production in 1975. Consumption of ammonium nitrate for all uses peaked in the United States in 1981 at 8.95 million metric tons; in 1986, apparent consumption dropped to only 6.31 million metric tons, of which 75° was used as fertilizer. By 1990, consumption had risen slightly to 6.64 million metric tons; total annual U.S. capacity in 1990 was 7.77 million metric tons. World ammonium nitrate capacity in 1985 was about 66 million metric tons, whereas reported consumption was about 44 million metric tons.

Ammonium nitrate fertilizer was priced at about \$137 t in bulk in June 1991. The DOT label required is OXY; the United Nations number is UN 1842.

Most ammonium nitrate manufactured for the explosives market is used in blasting agents prepared by adding a fuel component, such as diesel oil, to the prilled product. About 60° is consumed in coal mining; the remaining explosive markets are metal mining, nonmetal mining, quarrying, and highway construction.

A small but important use of ammonium nitrate is in the production of nitrous oxide; during the 1980s consumption for this purpose averaged about 30,000 t. The gas is generated by controlled heating of ammonium nitrate above 200°C. Nitrous oxide is used primarily as an anesthetic and as an aerosol propellant for food products (see ANESTHETICS; AEROSOLS).

Ammonium Nitrate Limestone

Many plants outside of North America prill or granulate a mixture of ammonium nitrate and calcium carbonate. Production of this mixture, often called calcium ammonium nitrate, essentially removes any explosion hazard. In many cases calcium nitrate recovered from acidulation of phosphate rock (see PHOSPHORIC ACID AND THE PHOSPHATES) is reacted with ammonia and carbon dioxide to give a calcium carbonate–ammonium nitrate mixture containing 21 to 26° nitrogen (23).

Ammonium Nitrite

Ammonium nitrite [13446-48-5], NH₄NO₂, a compound of questionable stability, can be prepared by reaction of barium nitrite and aqueous ammonium sulfate. After removal of the precipitated barium sulfate by filtration, the ammonium nitrite can be recovered from solution. The salt is said to decompose, sometimes explosively, at 60–70°C.

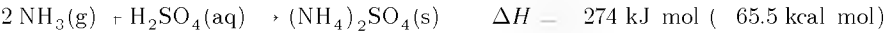
Ammonium Sulfate

Ammonium sulfate [7783-20-2], (NH₄)₂SO₄, is a white, soluble, crystalline salt having a formula wt of 132.14. The crystals have a rhombic structure; d₄²⁰ is 1.769. An important factor in the crystallization of ammonium sulfate is the sensitivity of its crystal habit and size to the presence of other components in the crystallizing solution. If heated in a closed system ammonium sulfate melts at 513 ± 2°C (14); if heated in an open system, the salt begins to decompose at 100°C, giving ammonia and ammonium bisulfate [7803-63-6], NH₄HSO₄, which melts at 146.9°C. Above 300°C, decomposition becomes more extensive giving sulfur dioxide, sulfur trioxide, water, and nitrogen, in addition to ammonia.

The solubility of ammonium sulfate in 100 g of water is 70.6 g at 0°C and 103.8 g at 100°C. It is insoluble in ethanol and acetone, does not form hydrates, and deliquesces at only about 80° relative humidity. The integral heat of solution of ammonium sulfate to saturation in water is 6.57 kJ mol (1.57

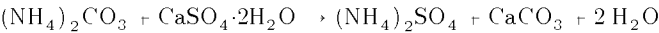
kcal mol) at 30°C; at saturation at the same temperature, the differential heat of solution is 6.07 kJ mol (1.45 kcal mol).

Manufacture. Ammonium sulfate is produced from the direct neutralization of sulfuric acid with ammonia; the heat of reaction is sufficient to evaporate all water if the concentration of the acid is 70% or higher.



Ammonium sulfate is also recovered as a by-product in large amounts during the coking of coal, nickel refining, and organic monomer synthesis, particularly during production of caprolactam (qv). About four metric tons of ammonium sulfate are produced per ton of caprolactam which is an intermediate in the production of nylon.

Some companies have used the Merseburg process to manufacture ammonium sulfate from gypsum, but the process is only economically attractive where sulfur is unavailable or very expensive (32), and is thus not used in the United States. Ammonium carbonate, formed by the reaction of ammonia and carbon dioxide in an aqueous medium, reacts with suspended, finely ground gypsum. Insoluble calcium carbonate and an ammonium sulfate solution are formed.



After removal of the calcium carbonate, the sulfate is recovered by evaporation and crystallization.

Some sulfuric acid producers use ammoniacal solutions to scrub tail gases from stacks in order to conform to federal and state regulations on sulfur dioxide emissions; ammonium sulfate is recovered as a product. Several similar scrubbing processes for removal of sulfur dioxide from electric power plant stack gas have been studied (33). However, such scrubbing operations could generate huge tonnages of ammonium sulfate, flooding local markets because long-distance shipment of the product is generally uneconomical.

Economic Aspects and Uses. Almost all ammonium sulfate is used as a fertilizer; for this purpose it is valued both for its nitrogen content and for its readily available sulfur content. In 1986–1987 United States consumption of ammonium sulfate was 0.57 million metric tons (34); world consumption during the same period was estimated at 13.3 million metric tons. In North America ammonium sulfate is largely recovered from caprolactam production.

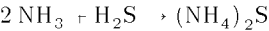
Ammonium sulfate is a good fertilizer for rice, citrus, and vines, and can be especially useful for some sulfur-deficient or high pH soils. Nonfertilizer uses include food processing, fire control, tanning, and cattle feed.

The price of standard ammonium sulfate was listed as \$61 per metric ton in bulk in June 1991.

Ammonium Sulfides

Ammonia combines with hydrogen sulfide, sulfur, or both, to form various ammonium sulfides and polysulfides. Generally these materials are somewhat unstable, tending to change in composition on standing. Ammonium sulfides are used by the textile industry.

Ammonium Sulfide. Ammonium sulfide [12135-76-1], (NH₄)₂S, can be produced by the reaction of hydrogen sulfide with excess ammonia.



Solid ammonium sulfide decomposes to ammonia and ammonium hydrosulfide at about 18°C; consequently it is normally marketed as a 40–44% aqueous solution. In June 1991 the price was \$507 per metric ton.

Ammonium Hydrosulfide. The reaction of equimolar amounts of ammonia and hydrogen sulfide results in the formation of ammonium hydrosulfide [12124-99-1], NH₄HS, which is also produced by the loss of ammonium from ammonium sulfide. The hydrosulfide is very soluble in water, liquid ammonia, liquid hydrogen sulfide, and alcohol. Solid ammonium hydrosulfide has a high vapor pressure, 99.7 kPa (748 mm Hg) at 32.1°C, and sublimates easily at ordinary temperatures. Vapors from the hydrosulfide, composed of ammonia and hydrogen sulfide, are very toxic.

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AMMONOLYSIS.

See AMINES.

AMORPHOUS MAGNETIC MATERIALS.

See AGNETIC MATERIALS, BULK.

AMOSITE.

See ASBESTOS.

AMPHIBOLE.

See ASBESTOS.

AMYL ACETATE.

See ESTERS, ORGANIC.

AMYL ALCOHOLS

Amyl alcohol describes any saturated aliphatic alcohol containing five carbon atoms. This class consists of three pentanols, four substituted butanols, and a disubstituted propanol, ie, eight structural isomers C₅H₁₂O: four primary, three secondary, and one tertiary alcohol. In addition, 2-pentanol, 2-methyl-1-butanol, and 3-methyl-2-butanol have chiral centers and hence two enantiomeric forms.

The odd-carbon structure and the extent of branching provide amyl alcohols with unique physical and solubility properties and often offer ideal properties for solvent, surfactant, extraction, gasoline additive, and fragrance applications. Amyl alcohols have been produced by various commercial processes in past years. Today the most important industrial process is low pressure rhodium-catalyzed hydroformylation (oxo process) of butenes.

Mixtures of isomeric amyl alcohols (1-pentanol and 2-methyl-1-butanol) are often preferred because the different degree of branching imparts a more desirable combination of properties; they are also less expensive to produce commercially. One such mixture is a commercial product sold under the name Primary Amyl Alcohol by Union Carbide Chemicals and Plastics Company Inc.

Physical Properties

With the exception of neopentyl alcohol (mp 53°C), the amyl alcohols are clear, colorless liquids under atmospheric conditions, with characteristic, slightly pungent and penetrating odors. They have relatively higher boiling points than ketonic or hydrocarbon counterparts and are considered intermediate boiling solvents for coating systems (Table 1) (1–16).

Table 1. The Amyl Alcohols and Some of Their Physical Properties

Properties	1-Pentanol	2-Pentanol	3-Pentanol	2-Methyl-1	3-Methyl-1	2-Methyl-2	3-Methyl-2	2,2-Dimethyl
				-butanol	-butanol	-butanol	-butanol	-1-propanol
CAS Registry Number	[71-41-0]	[6032-29-7]	[584-02-1]	[137-32-6]	[123-51-3]	[75-85-4]	[598-75-4]	[75-84-3]
common name	<i>n</i> -amyl alcohol	<i>sec</i> -amyl alcohol			isoamyl alcohol	<i>tert</i> -amyl alcohol		neopentyl alcohol
critical temperature, °C	315.35	287.25	286.45	291.85	306.3	272.0	300.85	276.85
critical pressure, kPa ^a	3868.	3710.	3880.	3880.	3880.	3880.	3960.	3880.
critical specific volume, mL mol	326.5	328.9	325.3	327	327	327	327	327
critical compressibility	0.25810	0.26188	0.27128	0.27009	0.26335	0.27992	0.27133	0.27745
boiling point at pressure, °C								
101.3 kPa ^a	137.8	119.3	115.3	128.7	130.5	102.0	111.5	113.1
40 kPa	111.5	93.8	90.9	103.5	105.6	78.3	87.2	89.0
1.33 kPa	44.6	32.0	27.7	40.2	43.0	21.0	26.0	25.0
vapor pressure ^b kPa ^a	0.218	0.547	0.761	0.274	0.200	1.215	0.810	0.929
melting point, °C	77.6	−73.2	−69.0	< 70	117.2	8.8	forms glass	54.0
heat of vaporization at normal boiling point, kJ mol ^c	44.83	43.41	42.33	44.75	43.84	40.11	41.10	41.35

ideal gas heat of formation ^d , kJ mol ^c	298.74	−313.80	−316.73	302.08	302.08	329.70	−314.22	−319.07
liquid density ^b , kg m ³	815.1	809.4	820.3	819.1	810.4	809.6	818.4	851.5 ^e
liquid viscosity ^b , mPa·s(cP)	4.06	4.29	6.67	5.11	4.37	4.38	3.51 ^d	2.5 ^e
surface tension ^b , mN m(dyn cm)	25.5	24.2	24.6	25.1 ^d	24.12	22.7	23.0 ^d	14.87 ^e
refractive index ^d	1.4080	1.4044	1.4079	1.4086	1.4052	1.4024	1.4075	1.3915
solubility parameter ^d (MJ m ³) ^{0.5f}	22.576	21.670	21.150	22.274	22.322	20.758	21.607	19.265 ^e
solubility in water ^b , wt %	1.88	4.84	5.61	3.18	2.69	12.15	6.07	3.74
solubility of water in ^b , wt %	9.33	11.68	8.19	8.95	9.45	24.26	11.88	8.23

^a To convert kPa to mm Hg, multiply by 7.5.

^b At 20°C unless otherwise noted.

^c To convert kJ mol to cal mol, multiply by 239.

^d At 25°C.

^e At the melting point.

^f To convert (MJ m³) to (cal)^{0.5}, divide by 2.045.

Commercial primary amyl alcohol is a mixture of 1-pentanol and 2-methyl-1-butanol, in a ratio of ca 65 to 35 (available from Union Carbide Chemicals and Plastics Company Inc. in other ratios upon request). Typical physical properties of this amyl alcohol mixture are listed in Table 2 (17).

Table 2. Physical Properties of Primary Amyl Alcohol, Mixed isomers^a

Property	Value ^b
molecular weight	88.15
boiling point at 101.13 kPa ^c , °C	133.2
freezing point, °C	90 ^d
specific gravity 20/20 °C	0.8155
absolute viscosity at 20°C, mPa·s(cP)	4.3
vapor pressure at 20°C, kPa ^c	0.27
flash point (closed cup), °C	45
solubility at 20°C, by wt %	
in water	1.7
water in	9.2

^a Ref. 17.

^b 65/35 blend, ie, a mixture of 1-pentanol and 2-methyl-1-butanol, 65/35 wt %, respectively.

^c To convert kPa to mm Hg, multiply by 7.5.

^d Sets to glass below this temperature.

Like the lower alcohols, amyl alcohols are completely miscible with numerous organic solvents and are excellent solvents for nitrocellulose, resin lacquers, higher esters, and various natural and synthetic gums and resins. However, in contrast to the lower alcohols, they are only slightly soluble in water. Only 2-methyl-2-butanol exhibits significant water solubility. As associated liquids, amyl alcohols form azeotropes with water and/or a variety of organic compounds (Table 3).

Table 3. Azeotropic Mixtures of Amyl Alcohols with Water^a

	Boiling point of azeotrope, °C ^b	Alcohol in azeotrope, wt %	Wt % alcohol	
			Upper layer	Lower layer
1-pentanol	95.93	43.65	84.29	2.54
2-pentanol	91.7	63.5		
3-pentanol	91.5	65	90.1	5.5
2-methyl-1-butanol	93.8	58.5		
3-methyl-1-butanol	94.82	50.67	84.15	2.96
2-methyl-2-butanol	87.35	72.5		
3-methyl-2-butanol	91.0	67.0		

^a Refs. 18–20.

^b At 101.13 kPa (1 atm).

Figures 1 and 2 show the relationship of viscosity and surface tension with temperature for various amyl alcohols. Curves for lower and higher alcohol homologues are shown for comparison.

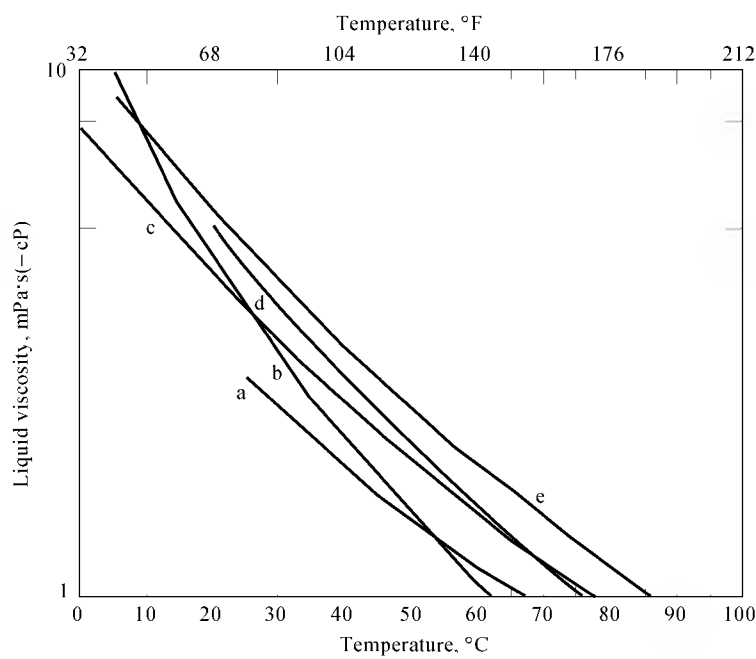


Fig. 1. Viscosities of amyl alcohols compared with 1-butanol and 1-hexanol (15). a, 1-butanol; b, 2-methyl-2-butanol; c, 1-pentanol; d, 2-methyl-1-butanol; e, 1-hexanol.

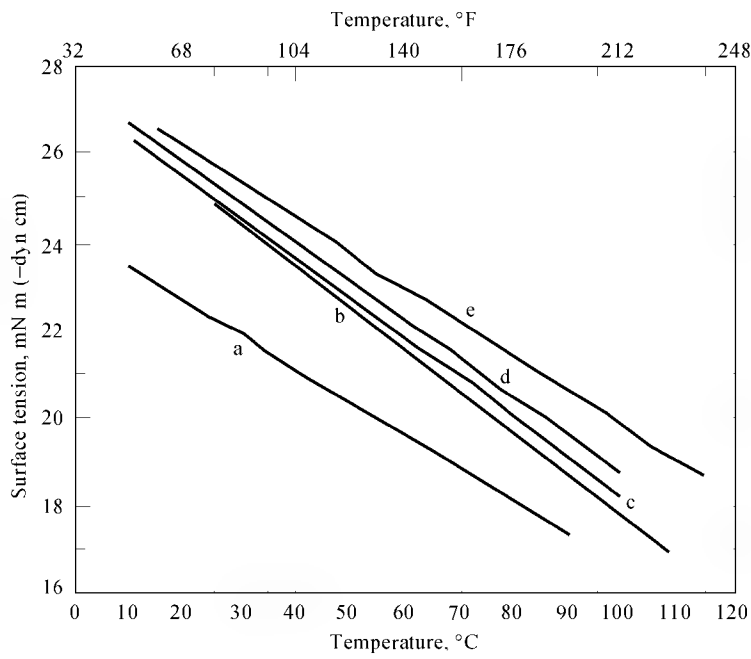


Fig. 2. Surface tension of amyl alcohols compared with 1-butanol and 1-hexanol (15). a, 2-methyl-2-butanol; b, 2-methyl-1-butanol; c, 1-butanol; d, 1-pentanol; e, 1-hexanol.

The physical characteristics of *tert*-amyl alcohol diverge from the standard trends for the other alcohols; it has a lower boiling point, higher melting point, higher vapor pressure, and low surface tension. Most notably, organic molecules are highly soluble in *tert*-amyl alcohol.

Chemical Properties

The amyl alcohols undergo the typical reactions of alcohols which are characterized by cleavage at either the oxygen–hydrogen or carbon–oxygen bonds.

Dehydration. Dehydration of amyl alcohols is important for the preparation of specialty olefins and where it may produce unwanted by-products under acidic reaction conditions. Olefin formation is especially facile with secondary or tertiary amyl alcohols under acidic conditions. The reverse reaction, hydration of olefins, is commonly used for the preparation of alcohols.

An example of a specialty olefin from an amyl alcohol is Phillips Petroleum's new process for 3-methyl-1-butene (used in the synthesis of pyrethroids) from the catalytic dehydration of 3-methyl-1-butanol (21,22). The process affords 94% product selectivity and 94% alcohol conversion at 310°C and 276 kPa (40 psig).

Dehydration of 1-pentanol or 2-pentanol to the corresponding olefins has been accomplished, in high purity and yields, by vapor-phase heterogeneous catalyzed processes using a variety of catalysts including neutral gamma–Al₂O₃ catalyst doped with an alkali metal (23), zinc aluminate (24,25), lithiated clays (26), Ca₃(PO₄)₂ (27) and montmorillonite clays (28). Dehydration of 2-methyl-1-butanol occurs over zinc aluminate catalyst at 270–370°C to give the expected 2-methyl-1-butene in high selectivities (24). The Al₂O₃ catalyzed process can be optimized to give di-*n*-pentyl ether as the exclusive product (23). Dehydration of 1-pentanol over an alkali metal promoted Al₂O₃ catalyst at 300–350°C provides 1-pentene at selectivities of 92% (29,30). Purification produces polymerization grade (99.9% purity) 1-pentene. A flow chart has been shown for a pilot-plant process (29).

Koch Reaction. C-6-neoacids are readily available from amyl alcohols by the Koch reaction. Greater than 95% 2,2-dimethylbutyric acid [595-37-9] was obtained from 2-methyl-1-butene at 304 kPa (3 atm) CO and 35°C for 1 h with cupric oxide and sulfuric acid catalyst (31). Likewise, 2,2-dimethylbutyric acid can be obtained in high yield (75–80%) from 1- or 2-pentanol or neopentyl alcohol from the Koch-Haaf reaction (32,33). *tert*-Amyl alcohol gives a mixture of trimethylacetic acid [75-98-9] (pivalic acid), 2,2-dimethylbutyric acid, C-7 acids, and C-11 acids under similar Koch-Haaf conditions (33).

Esterification. Extensive commercial use is made of primary amyl acetate, a mixture of 1-pentyl acetate [28-63-7] and 2-methylbutyl acetate [53496-15-4]. Esterifications with acetic acid are generally conducted in the liquid phase in the presence of a strong acid catalyst such as sulfuric acid (34). Increased reaction rates are reported when esterifications are carried out in the presence of heteropoly acids supported on macroreticular cation-exchange resins (35) and zeolite (36) catalysts in a heterogeneous process. Judging from the many patents issued in recent years, there appears to be considerable effort underway to find an appropriate solid catalyst for a reactive distillation esterification process to avoid the product removal difficulties of the conventional process.

Reaction of 1-pentanol with propionic acid provides 1-pentyl propionate [624-54-4], a new coatings solvent for automotive refinish and OEM paints, appliances, and for higher-solids systems (37). The esterification of 1-pentanol with formic acid to 1-pentyl formate [638-49-3] is conducted by concomitant removal of by-product water by azeotropic distillation with diethyl ether (38).

Alkali metal xanthates are prepared in high yield from reaction of amyl alcohols with alkali metal hydroxide and carbon disulfide (39–42). The xanthates are useful as collectors in the flotation of minerals and have minor uses in vulcanization of rubber and as herbicides (39,41).

Zinc dithiophosphates, which serve as antioxidants (qv) and antiwear agents in lubricants, are prepared by reaction of amyl alcohol and phosphorus pentasulfide followed by treatment with zinc sulfate (43).

Esters of *tert*-amyl alcohol can be obtained by acylation of 2-methyl-2-butene in the presence of trifluoromethanesulfonic acid (44). The esters produced, in high yields, from reaction of amyl alcohols with carboxylic anhydrides, are used as intermediates for preparation of pyrylium salts (45,46) and alkaloids (47). Triazoles prepared by acylation of 3-methyl-1-butanol are useful as herbicides (48).

Oxidation. Oxidation of the *n*-amyl alcohols produces aldehydes, which after continued oxidation can yield acids. This route to aldehydes has little merit. However, oxidative esterifications with alkali metal hypohalites (eg, calcium chlorite, Ca(OCl)₂) (49), bromates (eg, sodium bromate, NaBrO₃) (50) and halites (eg, sodium bromite, NaBrO₂) (51–53) have commercial potential. For example, a 90° yield of pentyl pentanoate [2173-56-0] was obtained from treatment of 1-pentanol with bromous acid or its salt in a solvent at pH 7–12 (53); sodium hypochlorite gave 87° yield of 3-methylbutyl isovalerate [659-70-1] from 3-methyl-1-butanol (49). Reaction is believed to involve dehydrogenation of an intermediate hemiacetal which, in turn, is formed from reaction of the first formed aldehyde with starting alcohol. Oxidation of secondary amyl alcohols afford high yields of ketones, eg, 3-pentanol gave 97° yield of diethyl ketone by oxidation with calcium hypochlorite (49).

Other examples of oxidation of amyl alcohols using hydrogen peroxide (54), RuO₂ NaClO (55), BaMnO₄ (56), and chromic acid (57,58) have been described for laboratory synthesis, but have not been utilized commercially.

Amination. Amyl alcohols can react with ammonia or alkylamines to form primary, secondary, or tertiary-substituted amines. For example, 3-methyl-butylamine [107-85-7] is produced by reductive ammonolysis of 3-methyl-1-butanol over a Ni catalyst at 150°C (59). Some diisoamyl- and triisoamylamines are also formed in this reaction. Good selectivities (88°) of neopentylamine [5813-64-9] are similarly produced by reductive ammonolysis of neopentyl alcohol (60).

Reaction of *tert*-amyl alcohol with urea in the presence of sulfuric acid gives a monoalkylated urea (61,62). Monoalkyl ureas are used to prepare uracil derivatives which are useful as herbicides, fungicides, and plant growth regulators (61).

Etherification. Ethers of amyl alcohols have been prepared by reaction with benzhydrol (63), activated aromatic halides (64), dehydration-addition reactions (65), addition to olefins (66–71), alkoxylation with olefin oxides (72,73) and displacement reactions involving their alkali metal salts (74–76).

The product benzhydrol pentyl ether [42100-71-0] from etherification of benzhydrol with 1-pentanol is utilized as low odor carrier oils for pressure-sensitive carbonless papers (63) and alkoxyated products are good surfactants (72). The *tert*-amyl functionality imparts pleasant aromas to compounds, eg, amyl substituted bicyclic polymethylated naphthalenones and indanones give fruity amberlike or woody aromas (69), and in acylhexamethylindans they provide a musklike odor (71), useful in perfumes. Ethers of neopentyl alcohol and 4-chlorobenzenethiol (4-thiophenyl neopentyl ether) are intermediates in the synthesis of thioether herbicide and plant growth regulators (64). Alkali *tert*-amyl alcoholates are useful in the preparation of colorfast pigments such as diphenylpyrrolopyroledione (75,76).

Condensation. The neopentyl trimethylolpropane carbonate [65332-76-5] formed from condensation of the trischloroformate of trimethylolpropane and neopentyl alcohol, is a clear yellow oil, useful as lubricant (77).

Methyl *t*-butyl ketone [1634-04-4] (pinacolone) has been prepared in 74° yield by reaction of *tert*-amyl alcohol with formaldehyde in the presence of strong acid catalyst (78,79).

The Guerbet reaction can be used to obtain higher alcohols; 2-propyl-1-heptanol [10042-59-8] from 1-pentanol condensation and 6-methyl-4-nonanol from 2-pentanol (80–83). Condensations with alkali phenolates as the base, instead of copper catalyst, produce lower amounts of carboxylic acids and require lower reaction temperatures (82,83). The crossed Guerbet reaction of 1-pentanol with methanol in the presence of sodium methoxide catalyst afforded 2-heptanol in selectivities of about 75° (84).

Friedel-Crafts alkylation of benzene with isomeric amyl alcohols proceeds with some rearrangement. For example, both 2- and 3-pentanol gave the identical product mixture (60° 2-phenylpentane, 31° 3-phenylpentane, and 9° *tert*-pentylbenzene) from reaction with benzene in the presence of BF₃ catalyst (85).

Reduction of 1-pentanol to pentane reportedly occurs during condensation of samarium with excess alcohol (86).

Other Reactions. Primary amyl alcohols can be halogenated to the corresponding chlorides by reaction with hydrogen chloride in hexamethylphosphoramide (87). Neopentyl chloride [753-89-9] is formed without contamination by rearrangement products. A convenient method for preparing *tert*-amyl bromide and iodide involves reaction of *tert*-amyl alcohol with hydrobromic or hydroiodic acid in the presence of Li or Ca halide (88). The metal halides increase the yields (85–95°) and product purity.

A method for the preparation of dipentyl carbonate from reaction of 1-pentanol with CO₂ in the presence of diethyl azodicarboxylate in high yields (81°) has been reported (89).

Neopentyl alcohol is useful for preparation of masked polyol silicate esters, capable of releasing the polyol under moisture conditions, in moisture-curable one-component liquid polyurethane compositions (90).

Manufacture

Three significant, commercial processes for the production of amyl alcohols include separation from fusel oils, chlorination of C-5 alkanes with subsequent hydrolysis to produce a mixture of seven of the eight isomers (Pennsalt) (91), and a low pressure oxo process, or hydroformylation, of C-4 olefins followed by hydrogenation of the resultant C-5 aldehydes.

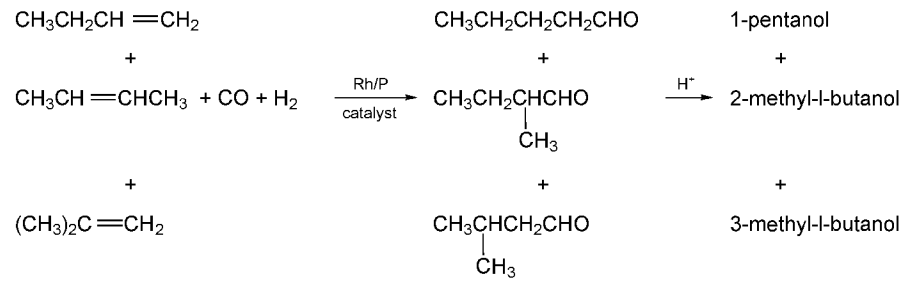
The oxo process is the principal one in practice today; only minor quantities, mainly in Europe, are obtained from separation from fusel oil. *tert*-Amyl alcohol is produced on a commercial scale in lower volume by hydration of amylenes (Dow, BASF) (92).

Fusel Oils. The original source of amyl alcohols was from fusel oil which is a by-product of the ethyl alcohol fermentation industry. Refined amyl alcohol from this source, after chemical treatment and distillation, contains about 85° 3-methyl-1-butanol and about 15° 2-methyl-1-butanol, both primary amyl alcohols. Only minor quantities of amyl alcohol are supplied from this source today. A German patent discloses a distillative separation process for recovering 3-methyl-1-butanol from fusel oil (93).

Chlorination-Hydrolysis Process. The first synthetic production of amyl alcohols was begun during the 1920s by the so-called chlorination-hydrolysis process in which a mixture of amyl chlorides is first produced by the continuous vapor-phase chlorination of a mixture of pentane and isopentane in the absence of light and catalysts. Hydrolysis of the chlorides with aqueous caustic at high temperatures produces a mixture of seven of the eight amyl alcohol isomers; formation of neopentyl alcohol is negligible. In contrast to the fusel oil and the oxo processes, this source provides significant quantities of the three secondary amyl alcohols, especially 2-pentanol. An excellent review with references and a process schematic has been published (91).

Oxo Process. Because of catalytic advances made since the 1970s in "oxo" chemistry and the comparatively high cost and waste disposal

problems associated with the chlorination-hydrolysis process, the oxo process (qv) is now the principal source of amyl alcohols. In the low pressure hydroformylation (oxo) process for the production of amyl alcohols, 1-butene, 2-butene, and 2-methyl-propylene (isobutylene) react with a mixture of carbon monoxide and hydrogen in the presence of a suitable metal catalyst (rhodium) to form an isomeric mixture of aldehydes with one more carbon atom than the olefin. Once made, the 1-pentanaldehyde [110-62-3] (*n*-valeraldehyde), 2-methylbutyraldehyde [96-17-3] and 3-methylbutyraldehyde [590-86-3] (isovaleraldehyde) are hydrogenated to the corresponding amyl alcohols.



Prior to 1975, reaction of mixed butenes with syn gas required high temperatures (160–180°C) and high pressures 20–40 MPa (3000–6000 psi), in the presence of a cobalt catalyst system, to produce *n*-valeraldehyde and 2-methylbutyraldehyde. Even after commercialization of the low pressure oxo process in 1975, a practical process was not available for amyl alcohols because of low hydroformylation rates of internal bonds of isomeric butenes (91,94). More recent developments in catalysts have made low pressure oxo process technology commercially viable for production of low cost *n*-valeraldehyde, 2-methylbutyraldehyde, and isovaleraldehyde, and the corresponding alcohols in pure form. The producers are Union Carbide Chemicals and Plastic Company Inc., BASF, Hoechst AG, and BP Chemicals.

Conventional triorganophosphite ligands, such as triphenylphosphite, form highly active hydroformylation catalysts (95–99); however, they suffer from poor durability because of decomposition. Diorganophosphite-modified rhodium catalysts (94,100,101), have overcome this stability deficiency and provide a low pressure, rhodium catalyzed process for the hydroformylation of low reactivity olefins, thus making lower cost amyl alcohols from butenes readily accessible. The new diorganophosphite-modified rhodium catalysts increase hydroformylation rates by more than 100 times and provide selectivities not available with standard phosphine catalysts. For example, hydroformylation of 2-butene with 1,1'-biphenyl-2,2'-diyl 2,6-di-*tert*-butyl-4-methylphenylphosphite ligand (P/Rh ratio of 10:1) achieves a rate of 12.85 mol (L·h) at 130°C, 0.2 MPa (30 psi) H₂, 0.2 MPa CO, producing a linear:branched C-5 aldehyde molar ratio of 1.13 (102). Hydroformylation of 2-butene provides a higher linear:branched aldehyde ratio (2.30) at 14.50 mol (L·h). Isobutene produces only 3-methylbutyraldehyde at 1.65 mol (L·h). Thus, new catalyst technologies have made it possible to increase the ratio of 2-methyl-1-butanol to 1-pentanol from 1- or 2-butene feedstock and provide commercially acceptable routes to 3-methyl-1-butanol at high rates and selectivities (103).

Typical specifications for commercially available amyl alcohols (104) are given in Table 4. The impurities typically present are other monomeric alcohols, dimeric alcohols, acetals, and several miscellaneous substances. The alcohols are substantially free of suspended matter.

Table 4. Specifications of Commercial Amyl Alcohols^a

	1-Pentanol	2-Methyl-1-butanol	Primary amyl alcohol mixed isomers
purity, wt % min			
1-pentanol	99.0, min	1, max	50–70
2-methyl-1-butanol		98.0, min	
amyl alcohols			98.0 min
3-methyl-1-butanol			0.01, max
2- and 3-methyl-1-butanols	0.5, max		
aldehydes, wt % max ^b		0.20	0.20
total carbonyl, wt %, max ^b	0.05		
unsaturation, wt %, max ^c		0.5	
distillation, °C ^d			
initial, min	135.0	126.0	127.5
dry point, max	139.0	139.0	139.0
acidity, wt %	0.005 ^e	0.01 ^f	0.01 ^f
water, wt %, max	0.2	0.3	0.20
specific gravity (20–20°C)			
min	0.814	0.815	0.812
max	0.818	0.822	0.819
color, Pt-Co	15	15	15

^a Ref. 104.
^b Calculated as C-5 aldehyde.
^c As pentenal.
^d At 101.3 kPa at 1 atm.
^e Calculated as valeric acid.
^f Calculated as acetic acid.

Hydration of Olefins. Several patents disclose the production of amyl alcohols by hydration of C-5 olefins (92,105–112). The Dow Chemical Company was the first to come on stream with such a process to produce *tert*-amyl alcohol. In the Dow process (92) *tert*-amyl alcohol is prepared by hydrating 2-methyl butenes in acetone over a cation-exchange resin catalyst distributed through all three reactors of a 3-stage reactor system. A single phase solution containing the reactants and solvent are fed to the first reactor, and the first reactor effluent and additional butene feed is then fed sequentially to the second and third reactors. The effluent from the third reactor is treated with an anion-exchange resin to remove acidic impurities and distilled to recover acetone solvent and remove part of the unreacted hydrocarbon overhead. The bottoms are distilled to recover acetone, unreacted butenes (which are recycled), and product alcohol. Solvent requirements are lowered by introducing additional butene before the second reactor.

Reduction of Acids. Patents claim catalysts for the hydrogenation of neoacids in the vapor-phase to the neoalcohols in good yields. For example, neopentyl alcohol has been prepared by passing pivalic acid (obtained by the Koch reaction of isobutylene) over a CuO-ZnO-Al₂O₃ catalyst at 250°C and 6.9 MPa (70.3 kg/cm²) in 100% selectivity (113). The neoalcohol was also produced in selectivities of 99% by employing zirconium hydroxide catalysts (114,115). The rates of the latter process, however, are reportedly low at liquid hourly space velocity (LHSV) of <1 kg catalyst-h. A catalyst from

Re₂O₇ and OsO₄ gave 94° neoalcohol at 100° pivalic acid conversion at 10 MPa (100 atm) hydrogen and 90°C (116). High yields are also obtained by the vapor-phase reduction of pivalic acid [75-98-9] with 2-propanol in the presence of zirconium oxide catalyst (117,118). Reduction with lithium aluminum hydride (119,120) also gives high yields but is less practical for commercial scale production. Production of neopentyl alcohol appears to be commercially viable, but this alcohol seems to be lacking significant large-scale applications.

Other Methods. As part of a considerable effort during the 1980s to make chemicals, such as acetic acid, ethanol, and ethylene glycol, from C-1 chemistry, some approaches to higher alcohols by either homologation of inexpensive alcohols (such as methanol) with syn gas or from syn gas alone were made. Essentially, this was a search for appropriate catalysts to provide desired conversions and selectivities to selected alcohols. For example, novel Ru–Mo–Na₂O catalysts supported on Al₂O₃ (121) and silica-supported molybdenum catalysts, promoted by KCl, (122) have high activity and good selectivities (up to about 70°) for a mixture of C-1–C-5 primary alcohols from syn gas. High temperatures (250–300°C) and pressures (10–50 MPa 1450–7250 psi) are required. A variety of other complex metal catalyst systems have been described such as Cu–Cr–Co–Rh (123), Cu–Co–Zn–Al₂O₃–K (124), Fe–Cr₂O₃ (125), Cu–ZnO (126), Cu–U–Al–K (127), Mo–W–Rh–K (128), and the like. Low yields to 1-pentanol are generally obtained. Efforts to homologize methanol to higher alcohols have been much less vigorous. Yields of C-5 alcohols were not much higher than from syn gas alone, but more conventional catalyst compounds of Co, Rh, Ru, and La were employed (129–132). Judging from the patent activity, the oil companies appear to be interested in this chemistry, but the results are not commercially viable at this time. There are several reviews on the subject of C-1 chemistry (133,134).

Health and Safety Factors

The main effects of prolonged exposure to amyl alcohols are irritation to mucous membranes and upper respiratory tract, significant depression of the central nervous system, and narcotic effects from vapor inhalation or oral absorption. All the alcohols are harmful if inhaled or swallowed, appreciably irritating to the eyes and somewhat irritating to uncovered skin on repeated exposure (135,136). Prolonged exposure causes nausea, coughing, diarrhea, vertigo, drowsiness, headache, and vomiting. Table 5 shows toxicity effects of amyl alcohols from animal studies (136). The toxicity of 3-methyl-2-butanol and 2,2-dimethyl-1-propanol has not been thoroughly investigated.

Table 5. Toxicity of Amyl Alcohols

	LD ₅₀ rats ^a , mg kg	LD ₅₀ rabbits ^b , g kg	LCL ₀ rats ^c , ppm 4 h	Eye injury, rabbits
1-pentanol	2200 ^d	3600 ^d	14000	20 mg 24 h moderate
2-pentanol	1470 ^e			20 mg 24 h moderate
3-pentanol	1870 ^d	2520 ^d		3 mg open severe
2-methyl-1-butanol	4920 ^d	3540 ^f		
3-methyl-1-butanol	1300 ^e	3212 ^d	150 ^g	20 mg 24 h moderate
2-methyl-2-butanol	1000			

^a Ingestion.
^b Skin penetration.
^c Inhalation.
^d No toxic effects noted.
^e Toxic effects not yet reviewed.
^f Primary irritation.
^g Sensory organs, lungs, and respiration irritation.

The C-5 alcohols are more toxic and narcotic than the lower homologues. Toxicity to rats from amyl alcohols decreases in the order: tertiary, secondary, primary. Toxicity of 3-methyl-1-butanol appears to have been studied the most. This alcohol caused a slight increase in cancerous tumors compared to controls in two studies (137,138). The tumors were located primarily in the stomach and liver.

The mean exposure limit value for 3-methyl-1-butanol in the air of workplaces was set at 100 ppm in 1984 by the ACGIH (135). Standards have not been set for the other alcohols (135).

Odor data for the various amyl alcohols is limited. The lowest perceptible limit for 1-pentanol and *tert*-amyl alcohol are 10 and 0.04 ppm, respectively (135). *tert*-Amyl alcohol has a threshold value of 2.3 ppm (and a 100° recognition level of 0.23 ppm); 3-methyl-1-butanol has an odor threshold of 7.0 ppm. The odor of 1-pentanol has been described as sweet and pleasant whereas that of 3-methyl-2-butanol is sour (135).

All of the amyl alcohols are TSCA and EINECS (European Inventory of Existing Commercial Chemical Substances) registered.

The amyl alcohols are readily flammable substances; *tert*-amyl alcohol is the most flammable (closed cup flash point, 19°C). Their vapors can form explosive mixtures with air (Table 6) (5,139–147).

Table 6. Flammability Limits of Amyl Alcohols^a

Alcohol	Flash point, °C		Flammability limits in air, vol °		Auto ignition temperature, °C
	Open cup	Closed cup	Lower	Upper	
1-pentanol	58	33	1.2	10	300.0
2-pentanol	42	34	1.5	9.7	343.33
3-pentanol	39	41	1.2	9.0	435.0
2-methyl-1-butanol	50	50	1.4	9.0	385
3-methyl-1-butanol	56	43	1.2	9.0	350
2-methyl-2-butanol	24	19	1.2	9.0	437.22
3-methyl-2-butanol	35	39	1.5	9.9	436.85
2,2-dimethyl-1-propanol		37	1.5	9.1	

^a Refs. 5, 139–147.

Shipping and Storage

Amyl alcohols are best stored or shipped in either aluminum, lined steel, or stainless steel tanks. Baked phenolic is a suitable lining for steel tanks. Plain steel tanks can also be used for storage or shipping. However, storage of aqueous solutions can cause rusting. Also, the alcohols are sufficiently hygroscopic so that moisture pick-up can cause rusting of plain steel storage tanks. Storage and transfer under dry nitrogen is recommended. Storage and handling facilities should be in compliance with the OSHA "Flammable and Combustible Liquids" regulations (17). Piping and pumps can be made from the same metals as used for storage tanks. The freezing points of amyl alcohols are low and they remain fluid at cold outside temperatures, thus allowing storage facilities above or below ground.

Economic Aspects

All eight amyl alcohol isomers are available from fine chemical supply firms in the United States. Five of them, 1-pentanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, and 2-methyl-2-butanol (*tert*-amyl alcohols) are available in bulk in the United States; in Europe all but neopentyl alcohol are produced (148,149).

Union Carbide Chemicals and Plastics Company Inc. is the only producer of C-5 oxo derived alcohols (148,150) in the United States. About 75° of the 30,000 t of valeraldehyde and 2-methylbutyraldehyde produced by the oxo process was converted to the isomeric mixture of primary amyl alcohols in 1988 (150). The primary amyl alcohol mixture was available in tank car quantities for \$1.02 kg in 1991. The Dow Chemical Company appears to have stopped commercial production of *tert*-amyl alcohol (151).

The demand for amyl alcohols is expected to remain unchanged until 1993. Competition from other alcohols and limited applications limit growth in markets for amyl alcohols. U.S. demand was predicted to grow from 29 × 10³ t in 1983 to 32 × 10³ t by 1990 (152). In Europe, amyl alcohols account for over 80° of the demand for valeraldehyde (17,000 t in 1984). BASF and Hoechst AG produce both *n*-valeraldehyde and 2-methylbutyraldehyde from butenes by the oxo process (149). The demand for C-5 in Europe is also predicted not to grow substantially (150). Amyl alcohols are growing at a much lower rate than other oxo alcohols as shown in Table 7.

Table 7. Production of Amyl Alcohols^a, 10³ t

Region	Alcohol	1980	1983	1988
United States	1-pentanol, 2-methylbutanol	23		23
Western Europe	1-pentanol, 2-methylbutanol	20	20	22

^a Ref. 150.
Courtesy of SRI International.

Uses

Table 8 summarizes domestic consumption by use for amyl alcohols. About 55° of the total 1-pentanol and 2-methyl-1-butanol production is used for zinc diamylthiophosphate lubrication oil additives (150) as important corrosion inhibitors and antiwear additives. Amyl xanthate salts are useful as frothers in the flotation of metal ores because of their low water solubility and miscibility with phenolics and natural oils. Potassium amyl xanthate, a collector in flotation of copper, lead, and zinc ores, is no longer produced in the United States, but imports from Germany and Yugoslavia were 910–1100 t in 1989 (150).

Table 8. U.S. Consumption of Amyl Alcohols^a 10³ t

Use	1979	1983	1987	1988
lube oil additives	11.4	11.4	10.5	9.5
solvent	3.6	2.7	3.2	3.6
amyl acetate	3.2	3.2	3.2	3.2
xanthates	0.91	0	0	0
flavors and fragrances	0.46	0.46	0.46	0.46
others	0.91	0.91	0.91	0.91
Total	20.18	18.67	18.27	17.67

^a Ref. 150.
Courtesy of SRI International.

Another significant application for amyl alcohols is for production of amyl acetates. Production of amyl acetates in 1987 is estimated to have been 4.5–5.5 × 10³ t; about 50° of the domestic demand is for lacquers (150). Union Carbide Chemicals and Plastics Company Inc. is the only U.S. producer.

As solvents, the amyl alcohols are intermediate between hydrocarbon and the more water-miscible lower alcohol and ketone solvents. For example, they are good solvents and diluents for lacquers, hydrolytic fluids, dispersing agents in textile printing inks, industrial cleaning compounds, natural oils such as linseed and castor, synthetic resins such as alkyds, phenolics, urea –formaldehyde maleics, and adipates, and naturally occurring gums, such as shellac, paraffin waxes, rosin, and manila. In solvent mixtures they dissolve cellulose acetate, nitrocellulose, and cellulosic ethers.

Primary amyl alcohol and its acetate ester are considered important medium-boiling nitrocellulose lacquer coating solvents. This mixture is a latent solvent and coupling agent for nitrocellulose lacquers. In blends, the solvent mixture modifies evaporation rate, lowers viscosities, improves blush resistance, and imparts improved flow and leveling which results in high gloss lacquer coatings.

The principal component of primary amyl alcohol, 1-pentanol, although itself a good solvent, is useful for the preparation of specific chemicals such as pharmaceuticals and other synthetics (153,154). Production of primary amyl acetate and its esters for solvent applications has seen low growth since the 1970s because of the decline of nitrocellulose lacquers and the introduction of new solvent systems.

Growth applications for amyl alcohols appear to be shifting toward higher boiling esters as plasticizers, perfumes, fragrances, and production of fine chemicals.

tert-Amyl alcohol is employed in formulations for stabilizing 1,1,1-trichloroethane (a replacement for trichloroethylene) which is used for degreasing metals, especially aluminum, copper, zinc, and iron and their alloys (151,155–158). The *tert*-amyl alcohol in stabilizing formulations allowed only negligible reaction between the 1,1,1-trichloroethane and metal. *tert*-Amyl alcohol is also used for stabilizing 1,1,1-trichloroethane mixtures for rosin flux removal compositions, eg, ionic and nonionic fluxes from circuit boards (159,160) and in stabilizer compositions for 1,1,1-trichloroethane for dry cleaning applications where it is durable against repeated use, without causing corrosion of the dry cleaner metal components and conforms with environmental and health standards enacted by the Occupational Safety and Health Act (161–163). *tert*-Amyl alcohol also has solvent use in the preparation of epoxy-containing novolak resins with low chloride content (164) and in mixtures with surfactants in enhanced petroleum recovery by flooding (165,166) (see PETROLEUM, ENHANCED OIL RECOVERY).

Other applications of amyl alcohols include their use as flavor and fragrance chemicals. Amyl isovalerate and amyl salicylate consumed a maximum of 450 t of amyl alcohols (150). Isoamyl salicylate is used to a large extent in soap and cosmetic fragrances because of its cost effectiveness (167). Isoamyl

alcohol is used as the extracting solvent for purification of wet process phosphoric acid. Total upgrading of 28–54° wet process phosphoric acid is achieved using this alcohol (168,169). *t*-Amyl methyl ether (TAME) is a useful gasoline additive as an octane booster (170,171). Amyl cinnamic aldehyde is an important ester of amyl alcohol (172). 1-Pentanol is used as an alcohol cosurfactant in a variety of applications (173,174). Amyl alcohols are used for the preparation of a variety of herbicides, fungicides, and pesticides. Amyl alcohols are a superior medium, compared to either benzyl alcohols or dichloromethane, for preparation of magnesia suspensions for electrophoretic deposition (175). Isoamyl alcohol is an intermediate in the synthesis of pyrethroids (21,22).

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AMYLAMINES.

See AMINES, ALIPHATIC, AMINES.

AMYLASES.

See ENZYME APPLICATIONS, INDUSTRIAL.

AMYLODEXTRINS.

See STARCH.

AMYLOPECTINS.

See STARCH.

AMYLOSES.

See STARCH.

ANALEPTICS.

See STIMULANTS.

ANALGESICS, ANTIPYRETICS, AND ANTIINFLAMMATORY AGENTS

Pain, pyresis, and inflammation are distinct physiological responses which can occur independently; they are often associated as the body mounts a response to an injury or insult. Each is an important signal from injured tissue and the signal's continued presence can guide a physician in diagnosing and treating the condition which led to the occurrence. Literature and folklore are replete with remedies which claim to alleviate aches and pains of all kinds. Whereas many treatments are baseless, some, especially those based on herbal medicines, serve as the basis for the rational discovery of the drugs that are used in Western medicine for treating pain and inflammation.

The twentieth century has seen considerable progress in the understanding of pain and inflammation and the relationship of one to the other. It is increasingly apparent that the central and peripheral nervous systems are capable of causing the production of mediators which can attract and activate inflammatory cells thereby initiating or amplifying an inflammatory response. At the same time, inflammatory cells are also capable of releasing substances which not only respond to the original insult, but also stimulate the nervous systems.

A number of interdependent physiological mechanisms, each providing new targets for therapeutic intervention, and allowing for the development of new treatments for pain, pyresis, and inflammation, have been discovered. At least eight distinct types of opioid receptors have been identified and the corresponding individual functions are beginning to be understood. Moreover, a great deal has been learned about the role of lipid mediators in the inflammatory response and how antiinflammatory agents control their production.

Endogenous Receptors and Ligands

In 1973 evidence was provided for the existence of receptors which recognize opioid molecules (1). As many as eight opioid receptors are known to exist, but only four, designated as μ (mu), κ (kappa), ς (sigma), and δ (delta), are believed to be important to the central nervous system (CNS). Several portions of the brain, including the hypothalamus and amygdala, the spinal cord, and nuclei concerned with vagal reflexes contain varying concentrations of the different types of opioid receptors.

The development of selective agonists and antagonists has aided in formulating a profile of pharmacological effects for each receptor type (2). The best understood is the μ receptor which plays a role in euphoria, respiratory depression, tolerance, and physical dependence as well as analgesic effects. Studies using highly selective agonists and antagonists imply that there may be μ receptor subtypes (3) suggesting that not all of the ascribed effects result from the same receptor. Antinociceptive activities and possible modulation of selected μ receptor activities can be identified. In addition to analgesia, the κ receptor effects include diuresis, sedation, and physical dependence (4). The effects of the δ receptor are less well understood as there is a lack of highly selective δ receptor ligands.

Shortly following the discovery of the opioid receptors, peptidic substances having opioid activity were detected in the pituitary gland (5). There are three known groups of endogenous opioid peptides: endorphins (6), enkephalins, and dynorphins (see OPIOIDS, ENDOGENOUS). Examples are given in Table 1. Every member of the three families is the progeny of a distinct polypeptide precursor. The endorphins are fragments of proopiomelanocortin [66796-54-1] (POMC), a polypeptide also containing β -lipotropic hormone, adrenocorticotrophic hormone (ACTH), and melanocyte stimulatory hormone (α -MSH) (8). β -Endorphin, the largest endogenous opioid peptide, is principally synthesized, stored, and ultimately released from cells in the pituitary gland as well as from neurons in the CNS. Although β -endorphin contains the sequence for met-enkephalin, $C_{27}H_{35}N_5O_7S$, the endorphin is not

processed to this enkephalin. Instead met-enkephalin is derived from proenkephalin, a polypeptide containing 6 met-enkephalins and 1 leu-enkephalin, C₂₈H₃₇N₅O₇ (9). These highly conserved, five amino acid peptides are located in the adrenal medulla, the CNS, and the peripheral nervous systems. Another polypeptide, prodynorphin also contains a leu-enkephalin fragment, as well as other peptidic opioids, including α- and β-neoendorphin and dynorphin A(1–17), C₉₀H₁₅₅N₃₁O₂₃. The latter is further cleaved to dynorphin A(1–8) and dynorphin B(1–3).

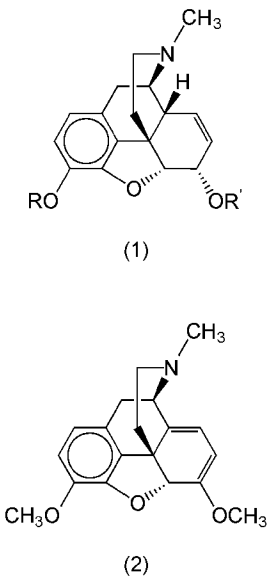
Table 1. Opioid Peptides

Compound	CAS Registry Number	Structural formula
β-endorphin	[60617-12-1]	H-TyrGlyGlyPheMetThrSerGluLysSerGlnThrProLeu-ValThrLeuPheLysAsnAlaIleValLysAsnAlaHisLysLysGlyGln-OH
leu-enkephalin	[58822-25-6]	H-TyrGlyGlyPheLeu-OH
met-enkephalin	[58569-55-4]	H-TyrGlyGlyPheMet-OH
dynorphin A(1–17)	[80448-90-4]	H-TyrGlyGlyPheLeuArgArgIleArgProLysLeuLysTrp-AspAsnGln-OH

When released, endogenous opioids act upon specific receptors, displaying effects like the quintessential opioid, morphine [57-27-2], C₁₇H₁₉NO₃. These endogenous peptides appear to induce analgesia and depress respiratory function, gastrointestinal transit, and several other physiological functions. Leu-enkephalin binds with relatively high selectivity to the δ receptor, dynorphin A(1–17) to the κ receptor. Like morphine, β-endorphin, and met-enkephalin are μ agonists. When administered intravenously, β-endorphin was three times more potent than morphine on a molar basis even though the large size and charged nature of β-endorphin should preclude its passage across the blood-brain barrier. The smaller enkephalins and dynorphins are potential substrates for peptidase degradation when administered systemically. Synthetic enkephalin analogues, designed to resist degradation, demonstrated analgesia in humans. Unfortunately, like morphine, these compounds do not cause analgesia without tolerance and physical dependence.

Opioid Agonists

Opium is the dried, powdered sap of the unripe seed pod of *Papaver somniferum*, a poppy plant indigenous to Asia minor. Theophrastus described its medical properties in the third century BC, but the Sumerians, ca BC 4000, probably perceived its utility. Arab physicians knew of the drug, and Arab traders carried it to the Orient where it was used as a treatment for dysentery. Paracelsus is credited with repopularizing the drug in western Europe in the early sixteenth century by formulating opium into "laudanum", which is still in use. More than 20 different alkaloids (qv) of two different classes comprise 25% of the weight of dry opium. The benzyisoquinolines, characterized by papaverine [58-74-2] (1.0%), a smooth muscle relaxant, and noscapine [128-62-1] (6.0%), an antitussive agent, do not have any analgesic effects. The phenanthrenes, the second group, are the more common and include 10% morphine (1, R' = R = H), 0.5% codeine [76-57-3], C₁₈H₂₁NO₃, (1, R' = H, R = CH₃), and 0.2 thebaine [115-37-7], C₁₉H₂₁NO₃, (2).



The correct structure of morphine, named after Morpheus, the Greek god of sleep, was first proposed in 1925 (10) and was confirmed in 1955 via total synthesis (11). Substitution at one or both of the two hydroxyl groups, one phenolic and the other allylic, give codeine, methyl morphine, where the substitution is on the phenolic hydroxyl, and heroin [561-27-3], C₂₁H₂₃NO₅, (1, R' = R = COCH₃), also known as 3,6-diacetoxy morphine, which serves as a prodrug and converts to morphine *in vivo*. Methylating both hydroxyl groups and introducing an additional double bond into the allylic ring leads to thebaine which has little analgesic action.

Morphine, mol wt 285.3, effectively relieves pain and increases an individual's ability to tolerate a painful experience. It also produces a remarkably broad range of other effects including drowsiness, and mood changes, respiratory depression, nausea, decreased gastrointestinal motility, and vomiting. Morphine behaves as a receptor agonist, acting preferentially at the μ receptor, but also exhibiting appreciable affinity for other opioid receptors. A standard therapeutic dose is 10–15 mg, usually administered subcutaneously. Analgesia peaks in about one hour and lasts for four to five hours. Morphine can also be administered orally, but it is only one sixth as potent. When delivered intravenously, morphine-induced respiratory depression is observed at below analgesic dose levels, as early as seven minutes after administration and for as long as 4–5 hours. An important feature of morphine and related drugs is the development of physical dependence on, and tolerance to, some of the effects. Increasingly large doses of drug must be administered to maintain the analgesic effects and the possibility of psychological dependence is a primary limitation to clinical use. However there are studies which suggest that when patients take morphine to combat pain, it is rare to see addiction, and thus morphine usage may be reasonable for the treatment of chronic pain (12). The cessation of drug uptake does produce withdrawal symptoms, such as diarrhea, vomiting, chills, fever, abdominal cramps, and abdominal pain, which are different from those observed during withdrawal from other CNS depressants. The onset and duration of symptoms depend upon the pharmacokinetic profile of the drug.

Codeine, mol wt 299.3, is a significantly less potent analgesic than morphine, requiring 60 mg (0.20 mmol) to equal the effectiveness of 10 mg (0.04 mmol) of morphine. However, codeine is orally effective, and it is less addictive and associated with less nausea than morphine. Codeine is used as an antitussive agent, although newer, nonaddictive agents are preferred (see EXPECTORANTS, ANTITUSSIVES, AND RELATED AGENTS).

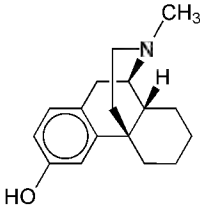
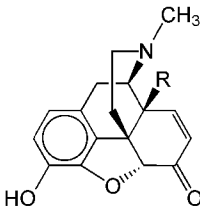
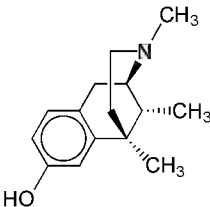
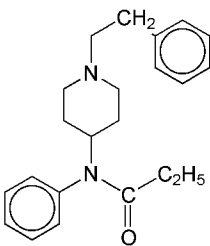
Introduced in 1898, heroin was heralded as a nonaddictive alternative to morphine. Subsequent clinical experience showed it to be highly addictive and preferred by addicts over morphine (13). Heroin is approximately ten times more potent than morphine, with quicker onset and shorter duration of

action. It is orally inactive, but is effective when administered intravenously. Although heroin has not been available in the United States for therapeutic use since 1906, it is still used clinically in other countries for its analgesic properties.

Synthetic and Semisynthetic Agonists

In attempts to discover drugs demonstrating fewer undesirable side effects than morphine, many synthetic analogues have been prepared. Some of these are shown in Table 2. The orally effective levorphanol (3) retains the complete morphine carbon skeleton, is more potent than morphine, and produces a correspondingly greater degree of respiratory depression (14). Oxymorphone (4, R = OH) and hydromorphone (4, R = H), both of which contain a C-6 carbonyl group, are more potent than morphine, but also produce greater side effects. Removal of one ring led to phenazocine (5), which is more potent than morphine and has the same duration of action, but is equally addictive.

Table 2. Synthetic Morphine Analogues

Name	CAS Registry Number	Molecular formula	Structure number	Structure
levorphanol	[77-07-6]	C ₁₇ H ₂₃ NO	(3)	
hydromorphoneoxymorphone	[466-99-9] [76-41-5]	C ₁₇ H ₁₉ NO ₃ C ₁₇ H ₁₉ NO ₄	(4, R = OH)(4, R = H)	
phenazocine	[127-35-5]	C ₂₂ H ₂₇ NO	(5)	
fentanyl	[437-38-7]	C ₂₂ H ₂₉ NO ₂	(6)	

Several common structural features necessary for opioid, analgesic activity have been identified from the action of the analogues. Systematic simplification demonstrated that much of the morphine ring structure could be modified or even eliminated. The piperidine ring, in a chair conformation, (Fig. 1) and in particular the nitrogen atom of that ring, appears essential to pharmacological activity. The nitrogen is believed to attach to an anionic center in the receptor. Also crucial is the presence of the phenyl ring which, through van der Waals forces, binds to the hydrophobic portion of the receptor. As in any receptor-ligand interaction, the stereochemistry of the chiral center shown in Figure 1 must be maintained.

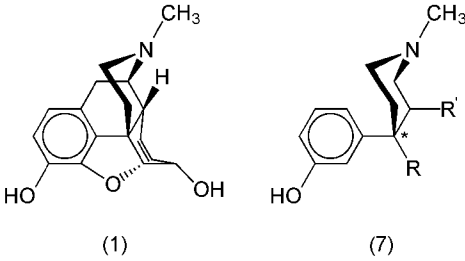
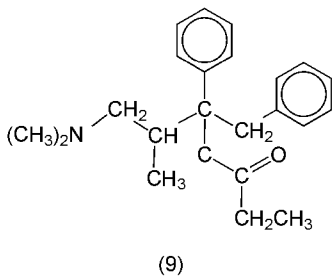
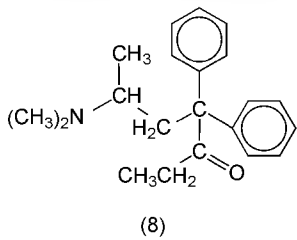


Fig. 1. Conformational representation of the piperidine ring of morphine (1) and analogues meperidine (7, R' = H, R = COOC₂H₅) and alphaprodine (7, R' = CH₃, R = OCC₂H₅). The chiral center of interest in structure (7) is starred (see text).

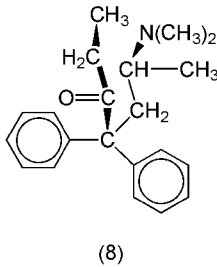
In the late 1930s, meperidine [57-42-1], C₁₅H₂₁NO₂, (Fig. 1) was identified as a potent μ receptor agonist (15). The later analogues, fentanyl (6) (Table 2) and alphaprodine [77-20-3], C₁₁H₂₃NO₂, (Fig. 1), also retain the key 4-phenyl piperidine ring structure. These agents appear to interact more strongly with the κ receptor than morphine, although they are still strong μ agonists. Fentanyl is more potent than morphine, has a much shorter duration

of action, and is used to aid the induction and maintenance of inhaled anesthesia. Meperidine and alphaprodine are less potent than morphine, requiring 75 (0.30 mmol) and 40 (0.15 mmol) mg, respectively, to equal the effectiveness of 10 mg (0.04 mmol) of morphine. However, they are more effective orally than morphine, without producing constipating or antitussive effects. Meperidine causes the same degree of respiratory depression as morphine at equivalent doses and is definitely addictive (16).

Phenylpropylamines are another structural class of receptor agonist. The two most important members are methadone [76-99-3], C₂₁H₂₇NO, (8) (17), discovered in Germany during World War II, and propoxyphene [469-62-5], C₂₂H₂₉NO₂, (9).



These compounds can adopt a conformation that mimics a disubstituted pseudopiperidine ring.

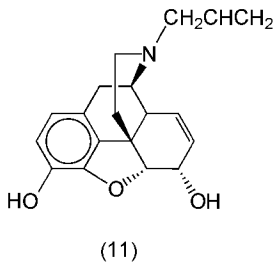
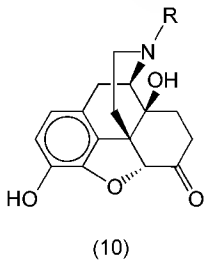


Methadone is orally active, having analgesic potency as great as morphine and longer duration of action. Although as potentially addictive as morphine, methadone causes less severe but more prolonged withdrawal symptoms and is therefore primarily used for the treatment of compulsive heroin users (18). In contrast, propoxyphene is a weak analgesic, only about half as potent as codeine and is often formulated with aspirin or acetaminophen, resulting in combinations which are more effective than either agent alone. Although propoxyphene has less potential for abuse than codeine, the actual incidence of abuse is equivalent, and hundreds of people die each year in the United States from overdoses.

Opioid Antagonists and Partial Agonists

The replacement of the *N*-methyl group on the nitrogen atom of the piperidine ring of morphine and analogues by allyl, isopropyl, or methyl cyclopropyl, an isopropyl isostere, results in compounds which antagonize opioid responses, especially respiratory depression. Naloxone [465-65-6], C₁₉H₂₁NO₄ (10

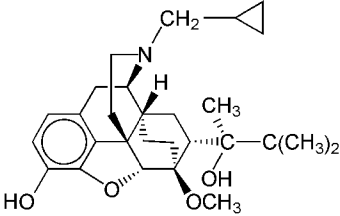
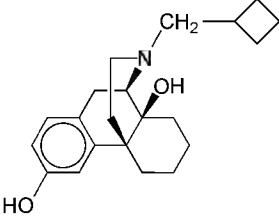
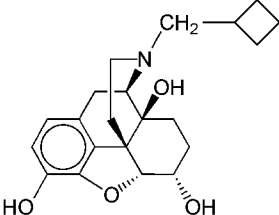
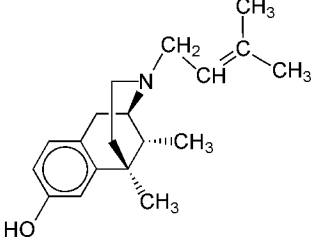
R = CH₂CHCH₂), and naltrexone [16590-41-3], C₂₀H₂₃NO₄ (10, $R = CH_2 \text{---} \triangle$), are both derived from oxymorphone (Table 2) and exhibit agonist activity only at doses that are of little clinical significance (19). In the absence of opioid drugs, naloxone does not cause analgesia, respiratory depression, or sedation. However, when administered with an opioid analgesic, the effects produced by the opioid agonist are promptly reversed. The ability to antagonize opioids at all of the different opioid receptors makes naloxone useful for the treatment of opioid overdose. As is typical for opioid antagonists, naloxone induces withdrawal symptoms in patients addicted to opiatelike drugs. Dosage is generally 0.4 mg (0.001 mmol) given intravenously in several doses because of the drug's short half life. Naltrexone has a similar profile, but it is orally active and has a significantly longer half life.



Before the introduction of naloxone, nalorphine [62-67-9], C₁₉H₂₁NO₃ (11) was the drug most often used for opioid overdose (20). Originally developed in the early 1940s, nalorphine is a morphine derivative and displays both agonist and antagonist properties. By itself, nalorphine causes typical agonist effects, analgesia and respiratory depression (21), but after administration of an opioid, such as morphine, it acts as an antagonist and negates the opioid's agonist effects (22). Its usefulness as an agonist is limited by the dysphoria it causes, and its use as an antagonist has been supplanted by the more effective naloxone.

The quest for compounds that combined the analgesic properties of morphine, were nonaddictive, and lacked the side effects of nalorphine, led to the development of the drugs shown in Table 3. These compounds have both agonist and antagonist activities. Nalbuphine (14) (23) and buprenorphine (12) (24) are semisynthetic materials derived from oxymorphone (4, R = OH) and thebaine (2) respectively, whereas pentazocine (15) (25) and butorphanol (13) (26) are benzomorphan and morphan derivatives. Although structurally similar, they display different receptor affinities: pentazocine is a weak μ-antagonist, but a strong agonist of the κ-receptor; nalbuphine is a competitive antagonist for the μ-receptor, blocking the effects of the morphinelike drugs, but is a partial agonist for the κ and σ receptors; and buprenorphine is a partial agonist for the μ-receptor.

Table 3. Drugs Exhibiting Both Opioid Agonist and Antagonist Activities

Compound name	CAS Registry Number	Molecular formula	Structure number	Structure
buprenorphine	[52485-79-7]	C ₂₉ H ₄₁ NO ₄	(12)	
butorphanol	[42408-82-2]	C ₂₁ H ₂₉ NO ₂	(13)	
nalbuphine	[20594-83-6]	C ₂₁ H ₂₇ NO ₄	(14)	
pentazocine	[359-83-11]	C ₁₉ H ₂₇ NO	(15)	

Pharmacologically, the effects of the drugs in Table 3 resemble those of opioid agonists. All four have analgesic potency equal to or greater than morphine and like morphine, they cause respiratory depression. A ceiling effect is reached, however, above which increased doses do not increase respiratory depression or do not produce proportionally greater depression. Buprenorphine causes a slow onset of the depression, and once the effects have begun, naloxone does not readily reverse the symptoms, suggesting that buprenorphine dissociates very slowly from opioid receptors. In all of these drugs except buprenorphine, high doses induce withdrawal symptoms in opioid dependent patients.

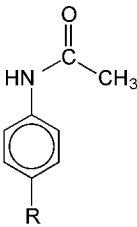
Other Analgesic Agents

Most analgesic agents rely on agonism of the μ receptor for their activity, however the ability of the κ and δ receptors to induce analgesia is also well documented (27). For example, the known μ receptor antagonist nalorphine is a κ agonist and still retains analgesic properties. Some nonmorphine analgesics which may preferentially bind to κ and δ receptors are found in Table 4. Spiradoline (19, X = H, Y = Cl), a κ agonist identified in preclinical studies, has good analgesic activity and little respiratory or gastrointestinal side effects (28,29). However spiradoline also produced sedative and psychomimetic effects in humans (30) preventing its development. No κ agonist has undergone rigorous clinical investigation, and the concept of a κ agonist analgesic as an alternative to morphine is not yet clinically validated.

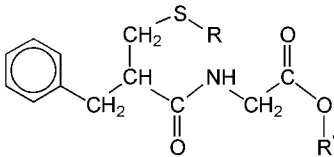
Table 4. Nonmorphine Analgesics

Name	CAS Registry Number	Molecular formula	Structure number	Structure
acetaminophenacet	[103-90-2]	C ₈ H ₉ NO ₂ C ₈ H ₉ NOC	(16, R = OH)(16, R =	

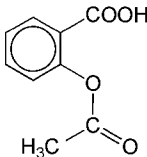
anilidephenacetin [103-84-4] 10H13NO2 H)(16, R OC2H5)



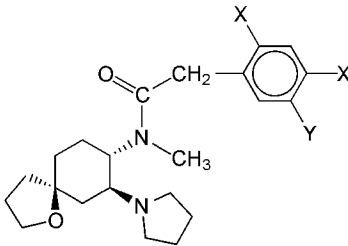
acetorphanthiorphan [81110-73-8] C21H23NO4SC12H15 (17, R = COCH3, R' = CH2C H5)(17, R H, R' H)



aspirin [50-78-2] C9H8O4 (18)



spiradoline [87173-97-5]a C22H30Cl2N2O2 (19, X = H, Y = Cl)



^a The Registry Number is for the monomethanesulfonate, CH₃SO₃H, salt.

Unselective and μ selective antagonists are well known, but there are few known selective κ receptor antagonists. The first of these, norbinaltorphimine [105618-26-6], (nor BNI), C₄₀H₄₃N₃O has 400-fold selectivity for κ over μ receptors and 250-fold for κ over δ (31). Two derivatives of spiradoline (19, X = H, Y = Cl) which lack the saturated furan ring, [125132-66-3], C₂₀H₂₇N₃OS, where X = NCS, Y = H, and [122407-13-0], C₂₀H₂₅Cl₂N₃OS, where X = NCS, Y = Cl, are site-directed, irreversible inhibitors of κ receptors, designed through modification of the spiradoline class of compounds (32). Although these drugs inhibit binding to κ receptors by 90%, they fail to bind all of the previously identified κ receptors, which suggests heterogeneity of the κ receptors.

It has also been suggested that the δ -receptor mediates analgesia. A synthetic peptide, D-Pen (2), D-Pen (5) enkephalin (DPDPE), a specific δ agonist (33), has produced analgesia in test animals, implying that agents of this type could be useful (34). Further studies demonstrated that mice deficient in μ , but not δ , receptors still perceive analgesia when given morphine or DPDPE thus confirming δ mediated analgesia (35). Administration of a δ selective enkephalin to morphine tolerant patients produced clinically significant pain relief, demonstrating that problems of tolerance may be avoided by using drugs of different pharmacological specificity (36). Although active *in vivo*, these drugs are rarely used systematically, because of very poor penetration of the blood brain barrier. The ability of an exogenous δ -receptor agonist to elicit meaningful analgesia in humans has not been demonstrated.

An alternative to the administration of exogenous analgesic agents is to encourage the stability of the endogenous agonists. The endogenous ligand, enkephalin, is enzymatically inactivated by enkephalinases (37) and a strategy to inhibit this event may increase its concentration and duration of action (see ENZYMES, INHIBITORS AND ANTAGONISTS). When administered intravenously, acetorphan, (17, R = COCH₃, R' = CH₂CH₃), a prodrug of thiorphan (17, R = R' = H), the first reported enkephalinase inhibitor, produced analgesia in post-myelography headache pain, but not in shock-induced pain (38). There was no tolerance or dependence observed.

Numerous neuropeptides are believed to be involved with the transmission or inhibition of pain, and the hope is to utilize this approach as a strategy to induce analgesia. Substance P is reported to be a transmitter of nociceptive impulses (39), and therefore antagonists should be analgesic. Capsaicin [404-86-4], C₁₈H₂₇NO₃, is known to deplete substance P and cause analgesia (40), but its side effects are intolerable. Antagonists to bradykinin [58-82-2], C₅₀H₇₃N₁₅O₁₁, a substance known to induce pain (41), have shown some success in preclinical trials.

Antiinflammatories and Antipyretics

Most of the time, the powerful analgesia supplied by morphine and the other opioid analgesics is not needed. Rather, a mild analgesic, such as aspirin, the most commonly employed analgesic agent, can be used for the treatment of simple pain associated with headaches, minor muscle pain, mild trauma, arthritis, cold and flu symptoms, and fever.

Aspirin, the oldest of the nonsteroidal antiinflammatory drugs (NSAIDs), is a member of the salicylate group. Salicyclic acid, isolated in 1838 from willow bark, was commonly used throughout the Middle Ages for the treatment of headaches. Its therapeutic benefits were well known even to Hippocrates. Many derivatives have been prepared to reduce the irritation associated with the pure acid. The most common form is acetylsalicylic acid [50-78-2] (18). Aspirin is an effective treatment for pain, fever, and for symptoms of acute inflammation. It is often the first treatment for the pain and swelling associated with rheumatoid arthritis. Because of its frequent usage, there are over 10,000 cases of serious salicylate intoxication in the United States every year. Many of these cases involve children, and some are fatal. High doses or chronic use of aspirin may aggravate peptic ulcer symptoms, generate gastric ulceration and bleeding, and produce acid-base and electrolyte imbalance.

Aspirin's pain relief results, not through direct action on the central nervous system, but rather through peripheral action. It has been proposed (42) that aspirin and aspirin-like drugs inhibit the enzymatic production of prostaglandins, a group of endogenous agents which are well known to cause erythema, edema, pain, and fever (43). Aspirin does not act as a prostaglandin receptor antagonist, rather it blocks the cyclooxygenase enzyme catalyzed conversion of arachidonic acid [506-32-1], C₂₀H₃₂O₂ to cyclic endoperoxides, a prostaglandin precursor as shown in Figure 2. Aspirin controls the synthesis and ultimately the release of prostaglandins from mammalian cells, producing an analgesic effect by decreasing the availability of prostaglandins which

typically potentiate the effect of bradykinin on receptors which mediate pain.

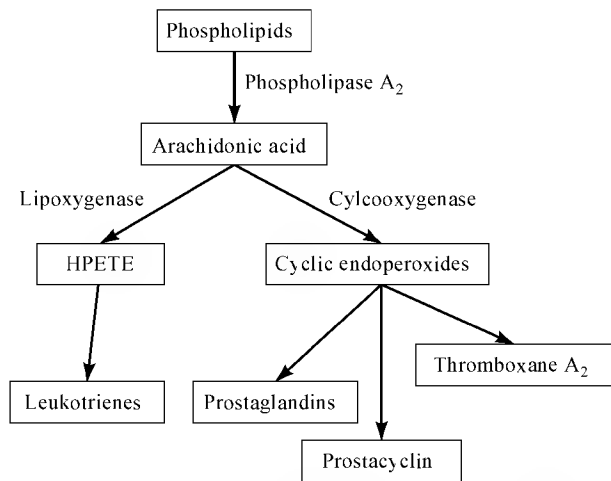


Fig. 2. Arachidonic acid cascade, HPETE = hydroperoxyeicosa-tetraenoic acids.

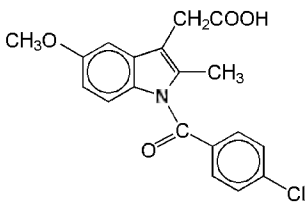
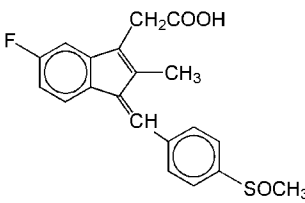
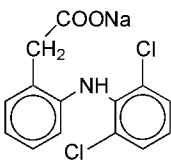
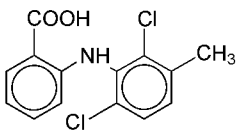
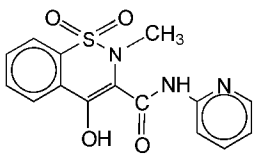
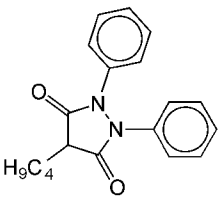
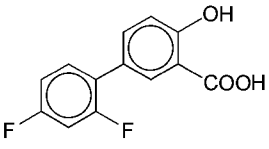
The action of endogenous pyrogens on the hypothalamus produces fever, because of a readjustment in the central set point controlling the body's internal temperature. Salicylates and other NSAIDs achieve their antipyretic effect by controlling the prostaglandin-induced release of pyrogens (44). However, hyperthermia induced by exercise, heat stroke, heat exhaustion, or drugs is not affected (45). In these cases the increased temperature is a result of insufficient heat loss. Salicylates block the synthesis of thromboxane A₂, which, in concert with prostacyclin [35121-78-9], controls platelet aggregation (46). The result is a decrease in the clotting rate, a condition which lasts long after the analgesic effects of aspirin and other NSAIDs have worn off and which can have serious consequences for those about to undergo surgery, but may be beneficial for those with a tendency towards thrombosis.

A second class of NSAIDs, the so-called coal tar analgesics, are derived from acetanilide (16, R = H). Although it is no longer used therapeutically, its analogues, phenacetin (16, R = OC₂H₅) and the active metabolite, acetaminophen (16, R = OH) are effective alternatives to aspirin (47). They have analgesic and antipyretic effects that do not differ significantly from aspirin, but they do not cause the gastric irritation, erosion, and bleeding that may occur after salicylate treatment. In contrast to aspirin, however, they are not cyclooxygenase inhibitors and have no antiinflammatory properties. Clinically acetaminophen is preferred over phenacetin, because it has less overall toxicity.

A more recently introduced, nonprescription analgesic is the aryl propionic acid, ibuprofen (20) (48), shown in Table 5, which offers significant advantages over aspirin. Ibuprofen, a cyclooxygenase inhibitor, displays good antiinflammatory activity. It is more potent than aspirin and has a lower incidence of gastrointestinal irritation, although at high doses or chronic exposure, gastric irritation, as well as some renal toxicity, has been observed. Ibuprofen is more effective than propoxyphene (9) in relieving episiotomy pain, pain following dental extractions, and menstrual pain.

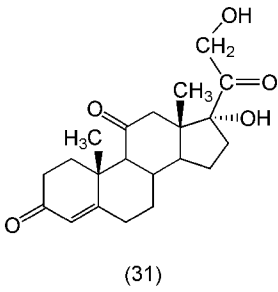
Table 5. Nonsteroidal Antiinflammatory Drugs

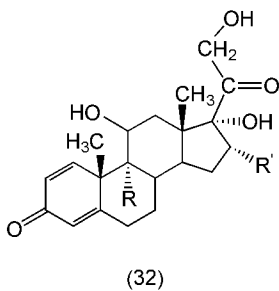
Name	CAS Registry Number	Molecular formula	Structure number	Reference	Structure
Aryl propionic acids					
ibuprofen	[15687-27-1]	C ₁₃ H ₁₈ O ₂	(20)		
naproxen	[22204-53-1]	C ₁₄ H ₁₄ O ₃	(21)	50	
ketoprofen	[22071-15-4]	C ₁₅ H ₁₄ O ₃	(22)	51	
flurbiprofen	[5104-49-4]	C ₁₅ H ₁₃ FO ₂	(23)	52	
Indoles					
indomethacin	[53-86-1]	C ₁₉ H ₁₇ ClNO ₄	(24)	53	

					
sulindac	[38194-50-2]	C ₂₀ H ₁₇ FO ₂ S	(25)	53	
					
diclofenac	[15307-79-6]	C ₁₄ H ₁₁ Cl ₂ NO ₂ Na	Fenamates (26)	54	
					
meclofenamate	[644-62-2]	C ₁₄ H ₁₁ Cl ₂ NO ₂	(27)	55	
					
piroxicam	[36322-90-4]	C ₁₅ H ₁₃ N ₃ O ₄ S	Others (28)	56	
					
phenylbutazone	[50-33-9]	C ₁ H ₂₀ N ₂ O ₂	(29)		
					
diflunisal	[22494-42-4]	C ₁₃ H ₈ F ₂ O ₃	(30)	57	
					

Ibuprofen only recently emerged from an ever growing collection of prescription NSAIDs (49) many of which are shown in Table 5. All of these drugs act by inhibiting the cyclooxygenase enzyme (Fig. 2) and there is little to distinguish in terms of analgesic effectiveness. When prescribed for the treatment of arthritis, patients require large doses for extended periods, exacerbating the side effects. Differences among drugs are found in dose levels, duration of action, and the incidence of gastric ulceration.

The adrenal cortex produces steroidal hormones that are associated with carbohydrate, fat, and protein metabolism, electrolyte balance, and gonadal functions (58). One of these, cortisone [53-06-5], C₂₁H₂₈O₅ (31), demonstrated a remarkable ability to relieve the symptoms of inflammatory conditions (59). Other glucocorticoid steroids, such as dexamethasone [50-02-2], C₂₂H₂₉FO₅ (32, R = F, R' = CH₃), and prednisolone [53-03-2], C₂₁H₂₈O₅ (32, R = R' = H), also have antiinflammatory properties.



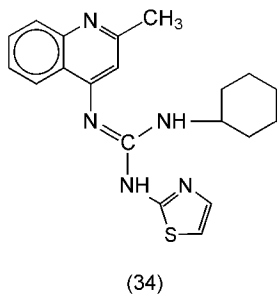
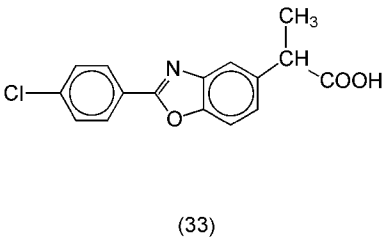


These steroids are capable of preventing or suppressing the development of the swelling, redness, local heat, and tenderness which characterize inflammation. They inhibit not only the acute symptoms of the inflammatory process, such as edema, fibrin deposition, and capillary dilatation, but also the chronic manifestations. There is evidence that glucocorticoids induce the synthesis of a protein that inhibits phospholipase A₂ (60), diminishing the release of arachidonic acid from phospholipids (Fig. 2), thereby reducing chemotaxis and inflammation.

Unfortunately steroids merely suppress the inflammation while the underlying cause of the disease remains. Another serious concern about steroids is that of toxicity. The abrupt withdrawal of glucocorticoid steroids results in acute adrenal insufficiency. Long term use may induce osteoporosis, peptic ulcers, the retention of fluid, or an increased susceptibility to infections. Because of these problems, steroids are rarely the first line of treatment for any inflammatory condition, and their use in rheumatoid arthritis begins after more conservative therapies have failed.

Analgesic antiinflammatory drugs having alternative mechanisms of action are under study. Whereas conventional therapies inhibit prostaglandin synthesis, other products of arachidonic acid metabolism (Fig. 2), such as the leukotrienes (LTs), have yet to be investigated. The 5-lipoxygenase enzyme begins a cascade of events which converts arachidonic acid to LTB₄, LTC₄, LTD₄, and LTE₄ (61). In particular LTB₄ plays a significant role in the recruitment of cells to the inflammatory site and is a potent mediator of immune responses. An antagonist of such a mediator might be efficacious in the treatment of inflammation.

The inhibition of both the lipoxygenase and cyclooxygenase pathways of arachidonic acid metabolism could offer improved therapy over conventional NSAIDs. Benoxaproten [51234-28-7], C₁ H₁₂ClNO₃ (33), a potent cyclooxygenase and lipoxygenase inhibitor, was introduced in 1982 (62). In clinical trials benoxaprofen showed good analgesic and antiinflammatory activity, but it was removed from the market within months of its release because of unacceptable levels of renal toxicity. The toxicity may not, however, have been related to the mechanism of action (63). Timegadinine [71079-19-1], C₂₀H₂₃N₅S (34), a drug having a similar mechanistic profile, is undergoing clinical trials (64).



Advances in the isolation and purification of lymphokine and monokine growth and differentiation factors offer the opportunity to interfere with the inflammatory process at the cellular level (65). The best understood factors are the interdeukins (1–9), tumor necrosis factor, and the interferons. Produced by activated macrophages, and other cells, interdeukin 1 (IL-1) is a local and hormonal mediator, which induces acute phase responses, local inflammation, and pyrogenicity. It is linked to rheumatoid arthritis, psoriasis, gingivitis, gout, islet destruction in diabetes, and wound healing (66). One of the principal functions of IL-1 is to induce the synthesis and release of interdeukin 2 (IL-2) (67). IL-2 is a T-cell growth factor, which stimulates the proliferation of T-cells and the release of numerous T-cell cytokines (68), thus amplifying the immune response. Interdeukin 4 is produced by T-cells, but acts principally on B-cells and enhances the B-cell's ability to present antigen to T-cells (69). Interdeukin 6 (IL-6) is produced by various cell lines upon stimulation with IL-1 or tumor necrosis factor. It acts as a B-cell growth and differentiation factor and acts in concert with interdeukin 3 to induce proliferation of pre B-cells in culture (70).

Economic Aspects

Analgesics and antiarthritics represent significant worldwide pharmaceutical markets. Table 6 lists trade names and producers of some of the more commercially important agents. The 1989 analgesic market was estimated at approximately \$4.0 billion. Of that figure, \$792 million is represented by opioid analgesics, whereas much of the nonnarcotic portion of the market is represented by NSAIDs. The 1989 antiarthritic market approached \$5 billion. Sales of prescription and nonprescription NSAIDs within this market were approximately \$4.5 billion. This figure includes both antiinflammatory and analgesic uses of these agents. The antiarthritic market is expected to continue to grow at a significant rate as the worldwide population ages.

Table 6. Trade Names and Procedures of Analgesics, Antipyretics, and Antiinflammatory Drugs

Compound name	Structure number	Trade name	Producer
levorphanol	(3)	Dromoran	Hoffman-LaRoche
phenazocine	(5)	Prinadol	Smith Kline & Beecham
meperidine	(7, R' H, R COOC ₂ H ₅)	Demerol	Winthrop
propoxyphene	(9)	Darvon	Eli Lilly
naloxone	(10, R CH ₂ CHCH ₂)	Narcan	Du Pont

naltrexone	(10, R = CH ₃ )	Trexan	Du Pont
nalbuphine	(14)	Nubain	Du Pont
buprenorphine	(12)	Buprenex	Norwich Eaton
pentazocine	(15)	Talwin	Winthrop
butorphanol	(13)	Stadol	Bristol
acetaminophen	(16, R = OH)	Tylenol	McNeil
ibuprofen	(20)	Motrin	Upjohn
naproxen	(21)	Naprosyn	Syntex
ketoprofen	(22)	Orudis	Wyeth
flurbiprofen	(23)	Ansaid	Upjohn
indomethacin	(24)	Indocin	Merck Sharpe & Dohme
sulindac	(25)	Clinoril	Merck Sharpe & Dohme
diclofenac	(26)	Voltaren	CIBA-GEIGY
meclufenamate	(27)	Meclomen	Parke-Davis
piroxicam	(28)	Feldene	Pfizer
diflunisal	(30)	Dolobid	Merck Sharpe & Dohme
benoxaprofen	(33)	Oralflex	Eli Lilly

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ANALYTICAL METHODS

Survey,
Trends,
Hyphenated Instruments,

SURVEY

Analytical methods are utilized by all branches of the chemical industry. Sometimes the goal is the qualitative determination of elemental and molecular constituents of a selected specimen of matter; other times the goal is the quantitative measurement of the fractional distribution of those constituents; and sometimes it is to monitor a process stream or a static system. Information concerning the various individual analytical methods may be found in separate articles dispersed alphabetically throughout the *Encyclopedia*. The articles are introductions to topics each of which is the subject of numerous books and other publications.

Analytical chemistry is an extremely broad discipline encompassing analytical strategy and data interpretation as well as techniques and instrumentation. Thus the analytical methods topics within the *Encyclopedia* may be roughly divided into six categories: articles on techniques such as the various spectroscopies, involving material characterization; articles on separation techniques, including some unit operations; articles on types of instrumentation and instrumental components; articles on nonspectrometric measurements, often used for monitoring; articles on sampling and on data analysis; and special purpose articles describing analytical methodology for specialized systems such as surfaces or residues. Methods for the analysis of a particular substance or group of substances can be found in the individual articles eg, see the analysis section in [ACETIC ACID](#); [HERBICIDES](#); [\(POLYHYDROXY\)BENZENES](#); and [TIN AND TIN ALLOYS](#)).

Materials characterization techniques, ie, atomic and molecular identification and analysis, are discussed in articles the titles of which, for the most part, are descriptive of the analytical method. For example, both infrared (ir) and near infrared analysis (nira) are described in [INFRARED AND RAMAN SPECTROSCOPY](#). Nuclear magnetic resonance (nmr) and electron spin resonance (esr) are discussed in [MAGNETIC SPIN RESONANCE](#). Ultraviolet (uv) and visible (vis), absorption and emission, as well as Raman spectroscopy, circular dichroism (cd), etc are discussed in [SPECTROSCOPY](#) (see also [CHEMILUMINESCENCE](#); [ELECTRO ANALYTICAL TECHNIQUES](#); [IMMUNOASSAY](#); [MASS SPECTROMETRY](#); [MICROSCOPY](#); [MICROWAVE TECHNOLOGY](#); [PLASMA TECHNOLOGY](#); and [X-RAY TECHNOLOGY](#)).

Some separation techniques articles discuss methods that may be applicable to samples that contain quantities of materials that are in microgram concentrations, such as [ELECTROPHORESIS](#) or high performance liquid chromatography (hplc) (see [CHROMATOGRAPHY](#)). Other articles describe techniques that can be used in the chemical process industry for the separation of metric ton-sized samples (see [DISTILLATION](#); [DISTILLATION, AZEOTROPIC AND EXTRACTIVE](#); [DIFFUSION SEPARATION METHODS](#); [EXTRACTION, LIQUID LIQUID](#); [EXTRACTION, LIQUID SOLID](#); [FILTRATION](#); [ION EXCHANGE](#); [REVERSE OSMOSIS](#); [SEPARATION, CENTRIFUGAL](#); [SEPARATION, MAGNETIC](#); [SEPARATION, SIZE](#); and [SEPARATION SYSTEMS SYNTHESIS](#)). Many of the special purpose articles also involve mixtures of materials and discuss separation techniques specific to the specialized system (see [BIOPOLYMERS, ANALYTICAL TECHNIQUES](#); [FORENSIC TESTING](#)).

Although instrumentation is discussed in many of the analytical articles, there are only a few places in the *Encyclopedia* where it is the primary emphasis (see [ANALYTICAL METHODS](#), [HYPHENATED INSTRUMENTS](#), [AUTOMATED INSTRUMENTATION](#)). However, articles relating to materials used either in or as instrumental components such as energy sources (see [LASERS](#)), sampling devices (see [FIBER OPTICS](#)), and detectors (see [BIOSENSORS](#); [PHOTODETECTORS](#); [SENSORS](#)) abound.

Both spectrometric and nonspectrometric methods are useful for monitoring systems for process or quality control, for environmental impact, and for other studies. Articles describing nonspectrometric measurements (see [FLOW MEASUREMENT](#); [LIQUID LEVEL MEASUREMENT](#); [PRESSURE MEASUREMENT](#); [RHEOLOGICAL MEASUREMENTS](#); and [TEMPERATURE MEASUREMENT](#)), and articles describing the use of analytical monitoring for particular systems (see [GROUNDWATER MONITORING](#); [MATERIALS RELIABILITY](#); [PROCESS CONTROL](#); [QUALITY CONTROL](#)) are to be found in the *Encyclopedia*.

The quality of an analytical result also depends on the validity of the sample utilized and the method chosen for data analysis. There are articles describing [SAMPLING](#) and automated sample preparation (see [AUTOMATED INSTRUMENTATION](#)) as well as articles emphasizing data treatment (see [CHEMOMETRICS](#); [COMPUTER TECHNOLOGY](#)), data interpretation (see [DATABASES](#); [IMAGING TECHNOLOGY](#)), and the communication of data within the laboratory or process system (see [EXPERT SYSTEMS](#); [LABORATORY INFORMATION MANAGEMENT SYSTEMS](#)).

Special purpose articles describe analytical methodology for specialized systems such as art objects, surfaces, or residues (see [FINE ART EXAMINATION AND CONSERVATION](#); [NONDESTRUCTIVE TESTING](#); [SURFACE AND INTERFACE ANALYSIS](#); and, [TRACE AND RESIDUE ANALYSIS](#)). Many of the techniques utilized for these systems are also discussed in materials characterization and separations articles. The methodology and some of the techniques are unique, however, and the emphasis in these special topics articles is on application to a particular system.

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TRENDS

Analytical chemistry, the science of the measurement and characterization of systems, is being revolutionized by the rapid advances in computer technology (qv), microelectronics, and materials science (qv). New techniques in chemical analysis, as well as significant developments in more established instrumentation and methodology, have resulted in the production of more analytical information of higher quality in less time than ever before. These developments are being driven by five separate factors: (1) the quest for truly automated or intelligent instruments (see EXPERT SYSTEMS); (2) the continued development of multidimensional hyphenated instruments, which involve the marriage of two instruments having complementary capabilities by way of a sampling interface and a common computer, thus facilitating the analysis of complex samples (see ANALYTICAL METHODS, HYPHENATED INSTRUMENTS); (3) continuous improvements in analyte detection limits bringing single atom analysis closer to reality; (4) increased capabilities in data manipulation, miniaturization of hardware, and remote *in vivo* sensing, leading to new instrumentation capable of both separation and specification; and (5) the development of nondestructible, stable, field-operable instrumentation utilizing fiber optic technology to serve as in-field sampling devices and process control (qv) tools (see FIBER OPTICS).

Intelligent Instruments

The use of "fixed" automation, automation designed to perform a specific task, is already widespread in the analytical laboratory as exemplified by autosamplers and microprocessors for sample processing and instrument control (see also AUTOMATED INSTRUMENTATION) (1). The laboratory robot originated in devices constructed to perform specific and generally repetitive mechanical tasks in the laboratory. Examples of automation employing robotics include automatic titrators, sample preparation devices, and autoanalyzers. These devices have a place within the quality control (qv) laboratory, because they can be optimized for a specific repetitive task. Application of fixed automation within the analytical research function, however, is limited. These devices can only perform the specific tasks for which they were designed (2).

Preferable in the analytical laboratory is "flexible" automation, ie, automation which can improve analysis efficiency, remotely control processes, automate analytical problem solving, and link other flexibly automated or intelligent instruments together in decision making. Instrumentation that has the ability to select an appropriate method, schedule a work program, develop a chemical method, self-optimize, do pattern recognition and decision analysis, fault alarm and self-diagnose, and repair itself is considered to be intelligent (3).

Microelectronics and microcomputers have made it possible to build flexible automated devices (4) leading to the introduction of programmable laboratory robots, which can perform a sequence of tasks within the domain of their mechanical capabilities. Developments in programmable automated instrumentation have turned into a launching platform for a fleet of new sophisticated instruments which are expected to appear in the marketplace during the 1990s (5). Changes at every stage of the analytical process are foreseen, ranging from sample preparation to analytical techniques and on into data interpretation.

There is a trend in the marketplace toward increasing instrumental flexibility through designing multitask capability. One way this increased versatility can be implemented is through the characterization end of an instrument, ie, through the sampling system and procedures, to the signal channel, and onto the detector transducer. Another way is through the instrument processing module, which includes the amplifier, processing functions, and readout. It is in this module that the next step in bringing the laboratory robot toward its full potential is expected to take place.

In the 1990s robotics guided by artificial intelligence are expected to play a role comparable to that of electronics in the 1940s and 1950s (6). Expert systems, which are knowledge-based systems that can effectively represent and apply factual knowledge in specific areas of human expertise, seem ideally suited to robot supervision.

Another step in laboratory automation to be achieved is the conversion of standard chemical procedures such as titrations or thermal gravimetric analysis, into unit laboratory operations. A procedure could then be selected from these laboratory operations by an expert system and translated by the system to produce a set of instructions for a robot. The robot should be able to obey specific instructions, such as taking a specified sample aliquot and titrating it using a specified reagent.

Evidence of the application of computers and expert systems to instrumental data interpretation is found in the new discipline of chemometrics (qv) where the relationship between data and information sought is explored as a problem of mathematics and statistics (7–10). One of the most useful insights provided by chemometrics is the realization that a cluster of measurements of quantities only remotely related to the actual information sought can be used in combination to determine the information desired by inference. Thus, for example, a combination of viscosity, boiling point, and specific gravity data can be used to characterize the chemical composition of a mixture of solvents (11). The complexity of such a procedure is accommodated by performing a multivariate data analysis.

Near infrared reflectance analysis (nira) is an example of an approach to automated characterization and intelligent instrumentation (12–15). In nira, which is used to examine complex samples, the resulting spectral pattern is heavily overlapped and spectral differences resulting from composition are barely observable. However, instead of resorting to conventional data reduction procedures, a combination of spectral correlation and a "self-teaching" algorithm is used. The procedure involves first measuring a set of preanalyzed samples, cross-correlating the spectra to composition using multilinear regression analysis, and using an optimization algorithm to select a set of measurement wavelengths and calibration coefficients for performing the analysis. Nira is capable of providing approximately 0.1% reproducible analysis utilizing spectral data in which gross compositional differences are barely observable. The power of such self-optimizing procedures, using the entire data set, goes much further than merely performing difficult measurements. A number of applications of the technique, such as in the analysis of grain and food products (16), have been successful in determining sample composition for which no known spectral feature, or no spectral feature at all, existed.

The ultimate goal of intelligent instrumentation is an automated system capable of accepting any type of sample and performing any analysis and characterization, such that all desired information would be obtained. Whereas such a highly flexible instrument clearly belongs to the future, more limited systems are already being developed along these lines.

Hyphenated Instruments

Multidimensional or hyphenated instruments employ two or more analytical instrumental techniques, either sequentially, or in parallel. Hence, one can have multidimensional separations, eg, hplc gc, identifications, ms ms, or separations identifications, such as gc ms (see CHROMATOGRAPHY; MASS SPECTROMETRY). The purpose of interfacing two or more analytical instruments is to increase the analytical information while reducing data acquisition time. For example, in tandem-mass spectrometry (ms ms) (17,18), the first mass spectrometer applies soft ionization to separate the mixture of choice into molecular ions; the second mass spectrometer obtains the mass spectrum of each ion.

Gc ms is an example of a hyphenated instrument consisting of two techniques that provide orthogonal (independent) information. If two independent techniques are linked in tandem, a large number of data resolution elements is obtained from each. The more dimensions present, and the higher the available resolution along each dimension, the greater is the obtainable information (19). Because hyphenated systems generate an immense

amount of data, serious hardware and software constraints are imposed on the data system. In addition, data processing systems also require enormous databases (qv) for rapid automatic data interpretation. Many of these databases are commercially unavailable and there is an obvious need for improvements in this area throughout the 1990s.

The use of pattern recognition (20,21) in automatic data interpretation provides an alternative to the development of huge databases. Most qualitative analysis procedures operate by recognition against databases, which therefore need to contain information about hundreds of thousands of compounds. Another approach involves the use of software to make molecular structure determinations from data through fundamental laws of physical chemistry and spectroscopy. This method allows qualitative data interpretation to become mostly independent of large databases. The difficulty lies in the extreme complexity of the programming, which involves the use of advanced artificial intelligence.

Hyphenated instrumental techniques that are commercially available include: gas chromatography mass spectrometry (gc ms) (22–25), liquid chromatography mass spectrometry (lc ms) (26,27), inductively coupled plasma mass spectrometry (icp ms) (28,29), and liquid chromatography gas chromatography (lc gc) (30). Among other techniques that are expected to become popular in the near future are capillary zone electrophoresis mass spectrometry (cze ms) (31,32), which is particularly suited for biological samples; gas chromatography atomic emission spectroscopy (gc aes) (33), a low cost technique for trace metals analysis; electrophoresis fluorescence (34), a combination of flow photometry and capillary electrophoresis technology; and liquid chromatography nuclear magnetic resonance (lc nmr) (35), a nondestructive technique for multicomponent analysis (see NONDESTRUCTIVE TESTING).

The possibilities for multidimensional instrumental techniques are endless, and many other candidate components for inclusion as hyphenated methods are expected to surface as the technology of interfacing is resolved. In addition, ternary systems, such as gas chromatography-mass spectrometry-infrared spectrometry (gc ms ir), are also commercially available.

Hyphenated analytical methods usually give rise to increased confidence in results, enable the handling of more complex samples, improve detection limits, and minimize method development time. This approach normally results in increased instrumental complexity and cost, increased user sophistication, and the need to handle enormous amounts of data. The analytical chemist must, however, remain cognizant of the need to use proper analytical procedures in sample preparations to aid in improved sensitivity and not rely solely on additional instrumentation to increase detection levels.

Extended Limits of Detection

Ultrasensitive detection capability is becoming more important in high purity materials development, geological and geochemical studies, and biological and environmental areas (see TRACE AND RESIDUE ANALYSIS). As a result, an ongoing task for the analytical chemist is to establish the smallest concentration at which a given substance can be detected. Previously, the more sensitive spectroscopic techniques enabled scientists to detect specific atomic and molecular ingredients of a sample at nanomolar (10^{-9} molar) levels. Improvements in sample inlet systems and in spectroscopic detection enabled picomolar (10^{-12} molar) quantities to be detected. The implementation of techniques such as radioimmunoassay and potentiometry allows for femtomolar (10^{-15} molar) detection, which represents millions of molecules (see IMMUNOASSAY).

As femtomolar detection of analytes become more routine, the goal is to achieve attomolar (10^{-18} molar) analyte detection, corresponding to the detection of thousands of molecules. Detection sensitivity is enhanced if the noise in the analytical system can be reduced. System noise consists of two types, extrinsic and intrinsic. Intrinsic noise, which represents a fundamental limitation linked to the probability of finding the analyte species within the excitation and observation regions of the instrument, cannot be eliminated. However, extrinsic noise, which stems from light scattering and or transient electronic sources, can be alleviated.

The use of laser (qv) radiation as an excitation source has had a major impact on analytical chemistry (36–39). A powerful, coherent, monochromatic laser source can serve a variety of applications, including sample-induced fluorescence and chemiluminescence (qv). Because ionization efficiency is high within the laser probe zone and because all ions can be collected and efficiently measured, the sensitivity of the method is high. Also, because ionization depends on resonant transitions of the analytes, a relatively high degree of selectivity is obtained.

An example of the use of lasers in optimizing analyte detection is provided by the technique of laser excited atomic fluorescence spectroscopy (leafs). The detection of subfemtogram amounts of cadmium, thallium, and lead has been reported (40). In this experiment, the sample of interest is first volatilized in a plasma (see PLASMA TECHNOLOGY) and then tuned photons from one or two dye lasers excite the analyte. When these atoms or ions relax, the resulting fluorescence signal is shunted into a photomultiplier for detection. Attomole detection levels are achievable using this technique. Continued advances in complex, multilaser spectroscopic determinations are expected to result in even lower levels of detection.

It is well known that fluorescence is one of the most sensitive techniques for chemical analysis (see SPECTROSCOPY). A molecule can undergo many excitation-emission cycles before it photochemically degrades. An application using laser fluorimetry with capillary zone electrophoresis has been reported to analyze amino acids at the attomolar range (41). Fluorescence analysis is made possible by employing the fluorescein [2321-07-5] isothiocyanate (fitc) derivative of a target amino acid. In this study, the analysis of a synthetic mixture of some 18 amino acids in the form of their fitc derivatives was performed. Detection limits ranged from 1.5×10^{-19} mol for lysine, to 9×10^{-21} mol for arginine. The extreme sensitivity and high resolving power of the method apparently led to the amino acid sequence determination of even minute quantities of proteins.

Another example of reducing the measurement volume to enhance detection sensitivity involves the observation of a single solution microdroplet (42). Micrometer-sized droplets can be generated on demand. These droplets have a high surface charge and thus can be trapped in an electrodynamic trap which holds the droplet stationary in space to within a fraction of its diameter. A laser beam is then employed to excite fluorescent molecules inside the droplet. The resulting fluorescence is measured by a photomultiplier assisted by supporting optics and electronics (see PHOTODETECTORS). The microdroplet approach offers such significant detection advantages as: independent control of the time of measurement, less diffusion of analyte from the analysis volume than in a flowing stream, and a possibly shortened fluorescence lifetime for a molecule confined to a droplet. The droplet may also act as an optical cavity, influencing the dynamics of photon emission and absorption. Reducing fluorescence lifetime can result in more signal photons per molecule and thus increased detection. Results indicated a detection limit in the range of 10^2 to 10^3 molecules assuming a signal to noise ratio of 2. Further improvements in detection may even be attained by measuring smaller droplets which would further reduce the background signal.

An alternative approach to trace analyte detection results from the measurement of chemiluminescence in a laser-generated plume of plasma, formed when the laser beam evaporates a small amount of sample (43). In these experiments, a pulsed excimer laser-induced-plasma, formed by laser vaporization and ionization, is probed directly to measure ion intensity. Ground state sodium atoms, excited state copper atoms, and sodium dimer molecules have all been monitored using this technique. This laser enhanced ionization may well be one of a very few techniques which can be used to probe extremely dense plasmas with good spatial and temporal resolution.

In addition to direct ion-measurement studies, the use of chemiluminescence as a detection method has also been investigated for elemental analyses using the laser microprobe (44). The chemiluminescence is produced by the reactions of analyte atoms formed in the laser plume with an ambient gas reagent. The chemiluminescence can then be measured directly, without either additional excitation or sample transfer, thus providing a simple and potentially quite sensitive method. This technique has been applied to studies of silicon, germanium, aluminum, and copper atoms in reactions with fluorine or fluorine-containing compounds. In the case of reaction between silicon and sulfur hexafluoride [2551-62-4], the limit of detection for silicon was approximately 10 picograms. Whereas this level of sensitivity is not as good as that which can be obtained by atomic emission techniques, continued reductions in background noise levels permit lower detection levels to be obtained.

Still another ultrasensitive detection method is provided by indirect detection of analytes (45,46). In indirect analysis an instrument does not respond to the presence of the species of interest, but rather monitors a decrease in the larger background signal as a means of detecting the presence of the analyte. Hence, one is actually measuring a negative response, rather than a positive one as in an emission peak. An example of this technique was demonstrated using microbore high pressure liquid chromatography, utilizing a polarimeter as a detector in the separation of octyl, allyl, and nonylphthalate plasticizers (qv). Using an optically active mobile phase containing limonene [138-86-3], $C_{10}H_{16}$, the three phthalates can be separated and quantitated down to part per trillion levels by observing the large shift in optical rotation exhibited by the optically active mobile phase as the background signal. The extension of this technique to more sensitive forms of detection, such as fluorescence, is expected to result in improvements in detection sensitivity (to attogram levels) as

well as dynamic range.

The extreme sensitivity and high resolving power of trace analysis techniques encourage the quest for single atom detection.

New Instrumental Techniques

Continued advances in analytical instrumentation have resulted in improvements in characterization and quantification of chemical species. Many of these advances have resulted from the incorporation of computer technology to provide increased capabilities in data manipulation and allow for more sophisticated control of instrumental components and experimentation. The development of miniaturized electronic components built from nondestructible materials has also played a role as has the advent of new detection devices such as sensors (qv). Analytical instrumentation capabilities, especially within complex mixtures, are expected to continue to grow into the twenty-first century.

Multidimensional Nmr Spectroscopy. An example of increased experimental capability through advances in data manipulation procedures is demonstrated with the advent of multidimensional nuclear magnetic resonance (nmr) techniques (see MAGNETIC SPIN RESONANCE) (47–50). By means of clever, sophisticated pulsed radio frequency excitation techniques, and advances in both computer hardware and software technology, it is possible to excite normally weak, multiple quantum transitions and to record nmr spectra in more than one dimension. The primary benefit derived from two-dimensional (2-D) nmr is confirmational information from spectral data which is lost in a conventional proton noise decoupled carbon-13 nmr experiment. In the 2-D case, spectra appear as contour maps where different types of interactions are spread out as resonances along two axes. In addition to the characteristic frequency shifts caused by nearest neighbors, the new dimension reveals more distant interactions. Thus conformational information can be determined for complex molecules without obtaining single crystals and x-ray structures. Multidimensional nmr is especially useful for biological molecules because it can give access to conformational information under conditions comparable to the *in vivo* environment.

The application of two-dimensional nmr techniques, the availability of high field (600 MHz) spectrometers, and the utilization of high speed mathematical and computational algorithms have enabled the advent of three-dimensional (3-D) nmr techniques for protein structure determination in solution. The resulting 3-D nmr spectrum is increased in complexity by another order of magnitude and structural analysis is extremely tedious and time consuming. Traditionally, nmr parameters for structural analysis involve the determination of chemical shifts (or ring current shift calculations), paramagnetic relaxation effects, vicinal coupling constants, and nuclear overhauser enhancement (NOE) effects. NOE arises from the fact that if two protons are separated by less than 0.5 nm, they can exchange magnetization with each other. This cross relaxation rate is proportional to $1/r^6$, where r is the internuclear distance. Hence, by perturbing the magnetization of one nucleus and watching its effect on the other, approximate internuclear distances can be obtained.

For a macromolecule such as a large protein, the steps in characterization involve, first, identification of the spin systems present, using correlated spectroscopy, and identification of neighboring amino acids. The long range noes are then assigned, and three bond coupling constants are determined. The secondary structure elements are then identified, and finally, the three-dimensional protein structure is obtained from the measured interproton distances and torsion angle parameters. This procedure requires a minimum of two days of nmr instrument time per sample, because two pulse delays are required in the 3-D experiment. In addition, approximately 20 hours of computing time, using a supercomputer, is necessary for the calculations. Nevertheless, protein structure can be assigned using 3-D nmr and a resolution of 0.2 nanometers is achievable. The largest protein characterized by nmr at this writing contained 43 amino acid units (51). However, attempts are underway to characterize the structure of interleukin #2 [85898-30-2], which has over 150 amino acid units.

Chemical Microsensors. Microsensor technology holds the promise of developing highly sophisticated chemical detectors which can both qualitatively and quantitatively quickly analyze the immediate environment for a variety of chemicals in spite of potential interferences at extremely low levels. Microsensor technology has already started to move away from the use of simple probes or electrodes coupled with chemically sensitive membranes, toward fully integrated solid-state sensing devices which have all of the electronic components etched on a single integrated chip.

A chemical microsensor can be defined as an extremely small device that detects components in gases or liquids (52–55). Ideally, such a sensor generates a response which either varies with the nature or concentration of the material or is reversible for repeated cycles of exposure. Of the many types of microsensors that have been described (56), three are the most prominent: the chemiresistor, the bulk-wave piezoelectric quartz crystal sensor, and the surface acoustic wave (saw) device (57).

Chemiresistors, as the name implies, are chemically sensitive devices that detect a change in the electrical resistance of a coating on the surface of a microsensor. The change occurs when the microsensor is exposed to a vapor-borne challenge. Solid-state chemiresistors are enjoying widespread applications in analytical laboratories. Some employ enzymes; others use ion-conducting polymers. Some chemiresistors are nonintegrated devices, ie, only the integrating device is on the chip; other chemiresistors are integrated sensors that consist of the detecting device plus various electronic components on the chip. Research in the area of chemiresistors is expected to aid any process requiring rapid, *in situ* identification and monitoring of chemical or biological species.

Bulk-wave piezoelectric quartz crystal sensors indirectly measure mass changes of the coating on the surface of the sensing device. This change in mass causes changes in the resonant frequency of the device, and measurements are based on frequency differences.

Surface acoustic wave (saw) devices are finding increasing use as chemical sensors and in a variety of applications. A saw device is a quartz plate having electrodes attached to its surface. Although they are similar to bulk-wave piezoelectric devices in that the mode of detection is based on a mass change of the coating on the surface of the device, the saw sensor operates using waves of higher frequency and, consequently, having greater sensitivity. Saw devices also possess several other advantages over bulk-wave piezoelectric sensors; including a greater ease of coating, uniform surface mass sensitivity, and improved ruggedness. Traditionally, the saw device has been used as a chemical vapor sensor responding to changes in mass, or in the conductivity of a thin film on its surface, caused by reaction with the impinging vapors. More recent experiments (58) indicate that the saw also responds to changes in the elastic properties of surface films. Thus these sensors can also be used to characterize solids such as polymeric materials.

In addition to chemical microsensors, studies indicate that sensors for biological and biomedical species, as well as other complex molecules that cannot be easily detected, should be commercialized in the 1990s (59). Biosensors (qv) utilize natural products, such as enzymes, cells, microorganisms, or plant tissue. Biosensors basically come in three types: immunological, biocatalytic, and sensory. Immunological biosensors take advantage of immunoreactions between immobilized antibodies and an antigen, bringing about cell lysis and allowing a detectable marker to escape from the antigen. Biocatalytic and sensory biosensors, however, provide measurement capability for a wider variety of complex molecules.

In Vivo Biosensing. *In vivo* biosensing involves the use of a sensitive probe to make chemical and physical measurements in living, functioning systems (60–62). Thus it is no longer necessary to decapitate an animal in order to study its brain. Rather, an electrochemical biosensor is employed to monitor intercellular or intracellular events. These probes must be small, fast, sensitive, selective, stable, rugged, and have a linear response. The microdialysis sampling process which allows the monitoring of small molecules in circulation within an animal, is an example. An artificial capillary is placed in the tissue region of interest, and a sample is collected via dialysis. In the case of a laboratory animal such as a rat, a probe is placed in the jugular vein under anesthesia. Flow rates are of the order of 1 $\mu\text{L min}$.

The advantages of *in vivo* biosensing are that the monitoring occurs inside a living species. Sampling rates are high, multiple analytes can be measured in the same location at the same time, and a wide range of analytical techniques can be employed for monitoring purposes. Concerns resulting from using this approach are that the living system is being perturbed for the measurement process, ie, removing chemicals from a living system disturbs its biology. Additionally, the region being sampled is not clearly defined, and very small volume samples are recovered. Nevertheless, the advantage of not having to sacrifice laboratory animals and the ability to make measurements on living systems make *in vivo* monitoring a potentially attractive assay technique.

Biomolecule Separations. Advances in chemical separation techniques such as capillary zone electrophoresis (cze) and sedimentation field flow fractionation (sfff) allow for the isolation of nanogram quantities of amino acids and proteins, as well as the characterization of large biomolecules (63–68) (see BIOPOLYMERS, ANALYTICAL TECHNIQUES). The two aforementioned techniques, as well as chromatography and centrifugation, are all based upon the differential migration of materials. Trends in the area of separations are toward the manipulation of smaller sample volumes, more rapid purification and analysis of materials, higher resolution of complex mixtures, milder conditions, and higher recovery (69).

The mode of operation of cze, a technique which is commercially available, is similar to conventional rod or slab electrophoresis, except that the

sample is introduced into an open tubular, 75–100 micrometer, fused-silica capillary. Use of the capillary enables on-column detection using one or more of a variety of on-line detectors, such as uv vis, fluorescence, electrochemical, and conductivity. In addition, this technique allows for the usage of higher electric fields than conventional slab gels. Higher applied voltage results in less diffusion and better resolution. A 10 theoretical plate efficiency is attainable.

Applications of cze include the detection of trace amounts of DNA and the separation of peptide fragments. Furthermore, this technique is beneficial to forensic scientists because restriction mapping can be performed, allowing assays for DNA to be carried out at the scene of a crime (see FORENSIC TESTING). It is also possible to interface capillary electrophoresis on-line with a mass spectrometer as a sample introduction technique in the analysis of amino acids and proteins (70). Further improvements in capillary electrophoresis include the need to increase column capacity. Most reported separations involve the resolution of only 20–30 components, whereas high resolution hplc is capable of resolving several hundred components in a mixture (see CHROMATOGRAPHY).

Sedimentation field flow fractionation (sfff) techniques are being implemented for molecular weight characterization of macromolecules (71,72). Sfff is capable of separations up to 10^{12} daltons and can also accommodate solid particulates. In contrast, gel permeation chromatography (gpc) has a separation range of up to approximately 10^7 amu, and electrophoresis to 10^9 amu. In sfff, an external centrifugal force field is applied to a sample pushing the material of interest against the wall of an empty channel. A laminar flow of solvent, which has a faster rate in the center than closer to the wall, is introduced. Thus, sfff is a separation mechanism which is independent of the shape of the molecule: small solutes elute first, larger ones later. This technique is really a combination of hplc and ultracentrifugation (see SEPARATION, CENTRIFUGAL). A knowledge of the material's density allows calculation of both mass and particle size distribution.

The sfff technique is versatile: it can be used to study both solids and solutions, no standards are required for calibration, and it is a nondestructive technique. Low shear forces are employed and minimal absorption occurs. Hence, sample degradation does not take place. The technique cannot, however, be routinely used for molecular weight characterization of small molecules. Newer variations of sfff include the development of thermal fff (73), whereby a temperature gradient is placed between two parallel metal blocks to allow the particles to migrate toward the wall. This approach is said to allow for the molecular weight characterization of polymeric materials which are much smaller in molecular size. Advantages of this technique over gpc lie in the absence of conventional band broadening effects.

Surface Characterization. Most modern techniques for the characterization of surfaces have been developed since 1970 (74,75). Surface techniques allow for both qualitative and quantitative characterization of trace levels of molecular species (see SURFACE AND INTERFACE ANALYSIS). Most recently an extension of surface analysis utilizing laser ionization has been introduced (76). In surface analysis by laser ionization (sali), a probe beam, composed of ions, electrons, or laser light, is directed to the surface under examination to remove a sample of material. An untuned, high intensity laser passes close to, but parallel and above the surface. The laser has sufficient intensity to induce a high degree of nonresonant, and hence nonselective, photoionization of the vaporized sample of material within the laser beam. The nonselectively ionized sample is then subjected to mass spectral analysis to determine the nature of the unknown species. A highlight of this technique is the use of efficient, nonresonant, and therefore nonselective photoionization by pulsed untuned laser radiation. The commercial availability of intense laser radiation makes this technique viable. The mass spectrometer, not the laser, performs the chemical differentiation.

An advantage of sali over a conventional surface analysis technique, such as secondary ion mass spectrometry (sims), is the feasibility of simple quantitative measurements. In addition, sali provides high sensitivity, mass resolution, and mass range, as well as a means of low damage analysis of organic surfaces. Sali is a versatile surface tool which can be applied to three-dimensional mapping of integrated circuits (qv), the chemical analysis of bulk synthetic polymer blends (qv), analysis of near-surface regions in passive films for corrosion prevention, and all kinds of biomedical materials analyses.

Analytical Instrumentation for Process Control

It is becoming more and more desirable for the analytical chemist to move away from the laboratory and into the field via in-field instruments and remote, point of use, measurements. As a result, process analytical chemistry has undergone an offensive thrust in regard to problem solving capability (77–79). *In situ* analysis enables the study of key process parameters for the purpose of definition and subsequent optimization. On-line analysis capability has already been extended to gc, lc, ms, and ftr techniques as well as to icp-emission spectroscopy, flow injection analysis, and near infrared spectrophotometry (80). In addition, new technology developments, such as on-line Raman spectroscopy, x-ray diffraction and gc lc are under commercialization for the 1990s.

One revolutionary *in situ* chemical monitoring method involves the use of a spectrophotometer coupled with fiber optics (qv) that transmit the analyzing light from the analyzer to the in-line sampling point, and back to the analyzer. In short, the fiber optics take the analyzer to the sample rather than the sample to the analyzer (81). No sample pretreatment or modification is required and measurements can be made in real time, under real process conditions of temperature, pressure, and environment. In addition, this technique helps to reduce the common analyzer problems related to sampling systems, eg, maintenance, transport, response times, and modified measurement conditions. Furthermore, the use of fiber optic signal paths, which are intrinsically safe and radio frequency interference (rfi) immune, enables analyte detection at distances as much as several hundred meters away from the sampling point. Detection is also possible at different locations simultaneously. Fiber optic probes have been employed for particle size analysis, uv vis nir spectrophotometers, and other photochemical processes, and applications of fiber optics in light scattering, absorption, and fluorescence experiments are in progress (82).

The advantage gained by using fiber optics for spectrophotometry are accompanied by certain limitations. Practical fibers are limited to a spectral range of approximately 200–2500 nm. This range is determined by the absorption characteristics of the silica used in the fiber's core. Although a number of materials have been developed for use further into the infrared, none provides the high transparency, low cost, chemical inertness, and physical toughness required for routine chemical applications.

The development of fiber optics technology, user-friendly displays, and enhanced data presentation capabilities have made on-line analysis acceptable within the plant manufacturing environment. However, it is apparent that a barrier still exists to some extent within many organizations between the process control engineers, the plant operations department, and the analytical function, and proper sampling is still the key to successful process analytical chemistry. The ultimate goal is not to handle the sample at all.

Analytical Capabilities

The increased demand for analyses in applications, such as industrial processes, the environment, and health, pushed worldwide sales of analytical instruments from \$300,000 to over \$3,000,000 during the 1980s (83). U.S. instrument manufacturers have also proliferated.

The analytical chemistry laboratory has successfully completed the transition from wet analysis to powerful and expensive instrumentation, but all problems cannot yet be solved using existing technology. For example, there is and will be an increasing need for more rapid and more definitive methods of isolation, purification, and analysis of proteins and other macromolecules, including advances in nucleic acid sequencing methods. The human genome project is expected to involve the investment of hundreds of millions of dollars. The development of instrumentation to expedite isolating and mapping the approximately one hundred thousand genes that comprise this gigantic project is a large analytical challenge.

Another vast field for the future is the analysis of organic molecules on surfaces. Whereas surfaces can be examined under high vacuum, in the real world surfaces are in contact with liquids and gases and these cannot be routinely explored using today's technology. Surface enhanced Raman spectroscopy (sers) can provide some of this type of information, but new techniques are needed to ascertain the nature of a species on the surface, eg, what form of arsenic is present and to what organic molecule does it belong. Quantitation of surfaces could result in higher spatial resolution, as well as the ability to map a surface microscopically as a function of both depth and breadth.

The biological and medical sciences are ripe for instrumentation advances. Whereas most immunoassays (qv) use radioactive materials, the implementation of chemiluminescent methods, enzyme techniques, and electrochemical methods is expected to become more important. New and better noninvasive methods of investigation are expected to become more routine. In addition, real-time measurements, whereby analyses of a number of

components in a biological system or the body are performed instantly, should also become available.

Refinement of existing techniques and instrumentation, rather than introduction of a whole new host of methods and instruments, is expected for the 1990s. One technology challenge is clearly the migration of analytical techniques out of the area of research and development and into the quality control and process control environments. Another challenge involves continued advances in smaller sample size, higher sensitivity and specificity, and lowered costs per sample analysis. Instruments should also become more user-friendly and more integrated within the total laboratory environment. Expert systems are expected to expand to the point where usage for both identification and quantification is routine in the analytical laboratory. Essential to this usage is the proper application of sampling (qv) and the understanding of chemistry.

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HYPHENATED INSTRUMENTS

In 1990, Chemical Abstracts' Service listed over 10 million substances in their Registry. Moreover, the growth of new compounds is exponential, leading to a doubling of known chemicals every eleven years. Thus there is an ever increasing need to efficiently identify substances and quantitate material with high confidence. Hyphenated instruments, combinations of accepted instrumental techniques where the sample is passed from one instrument directly into another, were developed to aid in solving this problem (1).

Hyphenated analytical methods provide more complementary information in a shorter time period leading to faster and more reliable results, than data obtained from traditional instrumental methods. The types of analytical instruments that can be joined is very large depending only upon the nondestruction of samples after the initial analytical procedure and the ability of the manufacturer to interface the instrumental techniques. Combinations include separation–separation, separation–identification, and identification–identification techniques (see ANALYTICAL METHODS, SURVEY).

Many of the more challenging analysis problems involve mixtures in a complex matrix. Thus an important first step is the ability to separate the components of these mixtures. Some of the earliest hyphenated techniques were those that coupled two separation methods, eg, gas chromatography–gas chromatography (gc–gc), and liquid chromatography–gas chromatograph (lc–gc) (see CHROMATOGRAPHY). For example, using lc–gc, small quantities of pesticides extracted from a crop can be determined. Samples are first injected into the lc where the majority of the matrix is separated out, then the "heart cut" of liquid containing the pesticide analyte is routed directly to the gas chromatograph for further separation and quantitation (see TRACE AND RESIDUE ANALYSIS).

Table 1 lists the most significant of the hyphenated instruments that were commercially available as of 1990. The instruments and methods discussed in detail herein all have both separation and identification capability.

Table 1. Commercially Available Hyphenated Instruments

Instrument ^a	Manufacturers	Price range, \$ × 10 ³	Estimated sales 1990 ^b , \$ × 10 ⁶
gas chromatograph–gas chromatograph (gc–gc)	Siemens AG, Carlo Erba	25	
gas chromatograph–liquid chromatograph (gc–lc)	Carlo Erba	35	
gas chromatograph–mass spectrometer (gc–ms)	Hewlett-Packard, Finnigan, VG Instruments, Varian	50–500	175
gas chromatograph–infrared spectrometer (gc–ir)	Hewlett-Packard, Nicolet, Digilab, Perkin-Elmer, Hewlett-Packard	70–250	26
gas chromatograph–atomic emission spectrometer (gc–ae)		90	
liquid chromatograph–mass spectrometer (lc–ms)	Hewlett-Packard, Finnigan, VG Instruments	130–300	25
mass spectrometer–mass spectrometer (ms–ms)	Finnigan, VG Instruments, Kratos, Extrel	250–500	258 ^c
gas chromatograph–mass spectrometer–infrared spectrometer (gc–ms–ir)	Hewlett-Packard	115	
super critical fluid chromatograph–infrared spectrometer (scfc–ir)	Nicolet, Digilab	100–200	
inductively-coupled plasma–mass spectrometer (icp–ms)	VG Instruments, Perkin Elmer	150–600	23

^a Whereas analytical techniques are often abbreviated using capital letters, *Encyclopedia* style is to use the lower case.

^b Strategic Directions International, Inc., Los Angeles, Calif.

^c Includes all quadruple and magnetic sector ms (no gc–ms) of which ms–ms is a subset.

Gas Chromatography/Mass Spectrometry

Mass spectrometry (qv) is the technique by which, utilizing electric and magnetic fields, ions are separated according to mass-to-charge ratios. The method of introducing an analyte into a mass spectrometer can be varied to accommodate gaseous, liquid, or solid samples. The combination of a gas chromatograph and a mass spectrometer (gc–ms) is particularly important because it can accommodate a wide variety of samples. The history of gc–ms dates to the late 1950s; many advances in this technique were made in the 1960s (2).

The combination of gas chromatography and mass spectrometry offers several advantages over the use of these techniques individually. Capillary gas chromatography provides very high separation efficiency for complex organic mixtures such as those found in environmental, foods and flavors, and general industrial applications. The mass spectrometer adds to this separation capability the unique ability to provide molecular structural information leading to both identification and quantitation of the separated components. Thus the gc–ms is a significant labor and time-saving device, accomplishing separation, component transfer, identification, and quantitation, often accompanied by a printed final report, all in a single instrument.

Instrumental Interfaces. The basic objective for any coupling between a gas chromatograph (gc) and a mass spectrometer (ms) is to reduce the atmospheric operating pressure of the gc effluent to the operating pressure in the ms which is about 10^{–3} kPa (10^{–5} torr). Essential interface features include: the capability to transmit the maximum amount of sample from the gc without losses from condensation or active sites promoting decomposition; no restrictions or compromises placed on either the ms or the gc with regard to resolution of the components; and reliability. The interface should also be mechanically simple and as low in cost as possible.

There are three common types of gc–ms interfaces: molecular separators, open split couplings, and capillary direct interfaces. Of the molecular separators, the two most often used are the jet separator (3) and the membrane separator (4,5). The jet separator shown in Figure 1 produces a jet spray out of the gc column effluent. Upon exiting the jet the effluent enters an evacuated chamber where the lower molecular weight components, including the majority of the gc carrier gas, are pumped away to the vacuum pump. The higher molecular weight components, having more momentum, are able to maintain a straight trajectory into the ion source of the mass spectrometer.

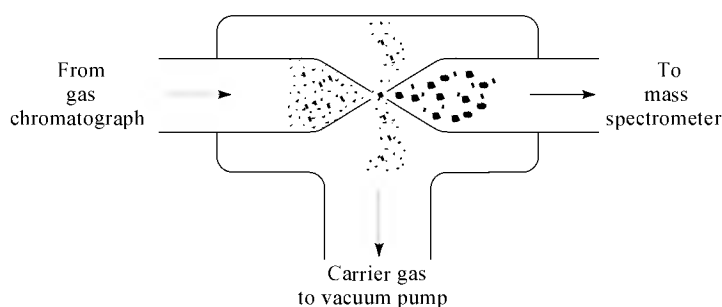


Fig. 1. Jet separator gc–ms interface.

In membrane separators a thin sheet of organic elastomer is used to selectively absorb organic compounds in the gc effluent and transmit them to the ion source. The permeability of an effluent component depends on its solubility in the membrane material and its diffusion constant. Gases such as helium, a gc carrier gas, have very low solubility in the membranes as compared to a substance such as decane, so the elastomer is generally an effective barrier for gc carrier gas. Membrane separators are often used for applications involving low molecular weight analytes because of the potential loss of these species in using the jet technique. For higher molecular weight compounds, the jet separator is most often used to avoid possible low solubility in the membrane.

One method of interfacing without the use of a molecular separator is employing an open split where a portion of the gc effluent is pumped away before entering the ms ion source (6). The open split technique has some advantages over the molecular separators including compatibility with all column sizes, easy column handling, wider choice of carrier gases including hydrogen, and lower cost. Disadvantages for the open split approach include line broadening that results from dead volume, potentially active surfaces, variable split efficiency with some discrimination favoring compounds of higher molecular weight, and sensitivity loss resulting from the split. The introduction in the 1980s of higher pumping capacity coupled with the widespread use of fused silica capillary gc columns, have led to another interfacing approach that is widely used, called the capillary direct interface. In this system, the gc capillary column is positioned directly into the ion source so that all of the gc effluent enters the ms. Advantages are high sensitivity, low dead volumes, and minimal sample decomposition or loss because of system inertness. A disadvantage of the capillary direct approach is that the choice of columns and carrier gas is dependent on the ms vacuum system pumping capacity. Additionally, changing gc columns becomes more time-consuming because of the requisite cooling and venting of the ion source.

Economic Aspects. The costs of gc–ms systems depend primarily on the type of mass analyzer used and the sophistication of the computer controlling the system (see COMPUTER TECHNOLOGY). Low end benchtop models controlled by a DOS-based personal computer cost around \$50,000. Midrange (\$100,000–250,000) machines may add higher mass range, a wider variety of ionization techniques, more pumping capacity, and more powerful multitasking computers. Then, at the high end, there are the magnetic sector-based systems which offer high resolution, mass spectra, and a price tag of \$250,000–500,000.

Applications. One of the most frequently used tools for systems requiring both qualitative and quantitative chemical analysis is gc–ms. It has been particularly valuable in the environmental field where laboratories responsible for the monitoring of hazardous compounds depend heavily on gc–ms to separate components of a usually complex mixture present in an environmental sample and then to identify and quantitate each component. One example is the analysis of semivolatile organics in drinking water (see GROUNDWATER MONITORING). This method, designated by the U.S. Environmental Protection Agency as Method 525 (7), requires full scan sensitivity down to 100 pg for 41 out of 43 target compounds. Drinking water contaminants are first concentrated using liquid–solid extraction cartridges which are eluted with a small volume of methylene chloride (see EXTRACTION, LIQUID–SOLID). The concentrated extract is then injected into the gc–ms to produce a total ion chromatogram (TIC) as shown in Figure 2 which also lists the target compounds for Method 525.

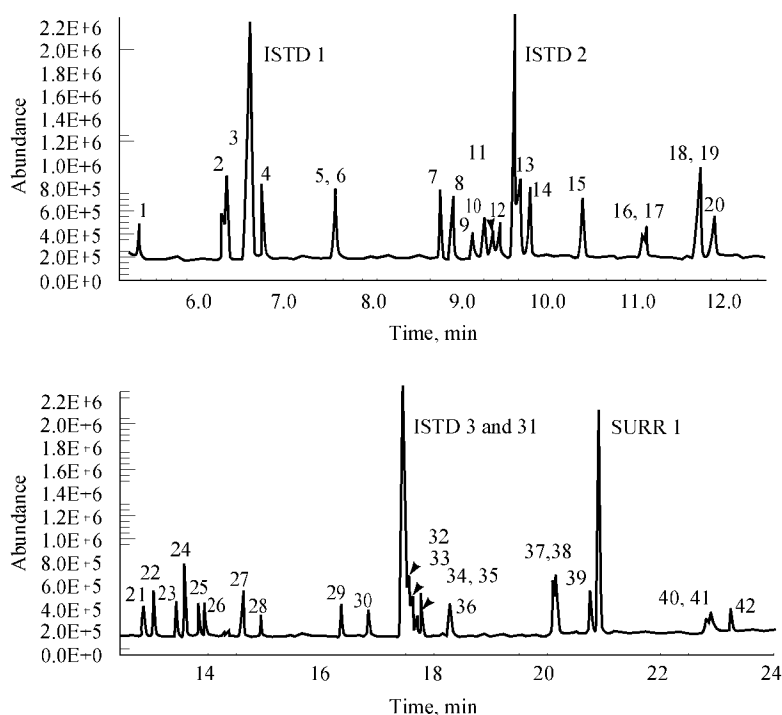


Fig. 2. Total ion chromatogram of drinking water. Analysis by EPA Method 525 using gc–ms. ISTD1 d_{10} -acenaphthene, ISTD2 d_{10} -phenanthrene, and ISTD3 d_{10} -chrysene are internal standards; SURR1 d_{12} -perylene is a surrogate splitless peak; and peaks 1–42 are 1. hexachlorocyclopentadiene, 2. dimethylphthalate, 3. acenaphthylene, 4. 2-chlorobiphenyl, 5. diethylphthalate, 6. fluorene, 7. 2,3-dichlorobiphenyl, 8. hexachlorobenzene, 9. simazine, 10. atrazine, 11. pentachlorophenol, 12. lindane, 13. phenanthrene, 14. anthracene, 15. 2,4,5-trichlorobiphenyl, 16. heptachlor, 17. alachlor, 18. di-*n*-butylphthalate, 19. 2,2',4,4'-tetrachlorobiphenyl, 20. aldrin, 21. heptachlor epoxide, 22. 2,2',3',4,6-pentachlorobiphenyl, 23. gamma-chlordane, 24. pyrene, 25. alpha-chlordane, 26. *trans*-nonachlor, 27. 2,2',4,4',5,6'-hexachlorobiphenyl, 28. endrin, 29. butylbenzylphthalate, 30. di(2-ethylhexyl)adipate, 31. benz[*a*]anthracene, 32. chrysene, 33. 2,2',3,3',4,4',6-heptachlorobiphenyl, 34. methoxychlor, 35. 2,2',3,3',4,5',6,6'-octachlorobiphenyl, 36. di(2-ethylhexyl)phthalate, 37. benzo[*k*]fluoranthene, 38. benzo[*b*]fluoranthene, 39. benzo[*a*]pyrene, 40. indeno[1,2,3-*c,d*]pyrene, 41. dibenz[*a,b*]anthracene, 42. benzo[*g,h,i*]perylene.

Important to environmental analysis is the ability to automate the injection, as well as the identification and quantitation of large numbers of samples. Gc/ms systems having automatic injectors and computerized controllers have this capability, even producing a final report in an unattended manner. Confirmation and quantitation are accomplished by extracting a specific ion for each of the target compounds. Further confirmation can be obtained by examining the full scan mass spectrum.

A technique that is related to gc/ms and starting to grow significantly in use is that of inductively coupled plasma mass spectrometry (icp/ms). In icp/ms the inductively coupled plasma serves as a good interface and ion source for the quadrupole mass spectrometer (see PLASMA TECHNOLOGY). Trace elemental analysis of very complex mixtures are possible using icp/ms. Anything that is introduced to the plasma is totally and cleanly ionized to elemental form, then passed into the mass spectrometer for identification. Gold has been determined at the femtogram level in seawater using flow injection icp/ms (8).

Gas Chromatography/Infrared Spectroscopy

Gc/ir instruments are all of the gc/fir variety that utilize an interferometer and require a Fourier transform of the signal as opposed to employing a monochromator and mechanical scanning. At least 3 scan/second are needed across the capillary gc peaks which are from 3 to 6 seconds wide.

Instrumental Interface. Gc/fir instrumentation has developed around two different types of interfacing. The most common is the on-the-fly or flow cell interface in which gc effluent is directed into a gold-coated cell or light pipe where the sample is subjected to infrared radiation (see INFRARED AND RAMAN SPECTROSCOPY). Infrared transparent windows, usually made of potassium bromide, are fastened to the ends of the flow cell and the radiation is then directed to a detector having a very fast response-time. In this light pipe type of interface, infrared spectra are generated by ratioing reference scans obtained when only carrier gas is in the cell to sample scans when a gc peak appears.

Another type of gc/fir interface involves trapping the components as they elute from the gc column. The gc effluent is deposited onto a zinc selenide plate at liquid nitrogen temperature, then the deposited trace of effluent is moved into the optical path of a standard fir spectrophotometer. A variation of this approach is referred to as matrix isolation: the gc effluent is trapped in a matrix of argon on a gold-coated drum at liquid helium temperature. Advantages of isolation interfaces over the flow cell design are about an order of magnitude increase in sensitivity (in the range of tens or a hundred picograms for a given component), and the ability of the user to search condensed phase spectral libraries that are larger than vapor phase libraries (see DATABASES; INFORMATION RETRIEVAL). Disadvantages include the complexity of the systems leading to lower sample throughput and much higher price.

Gas Chromatography/Mass Spectrometry/Infrared Spectroscopy

Gas chromatography/fourier transform infrared spectroscopy (gc/ftir), itself a very useful analytical technique, is especially powerful when combined with mass spectrometry (9,10). One of the factors in making the ternary gc/ir/ms system a viable analytical tool was the development of faster, more powerful computers to acquire, analyze, and report the large quantities of data generated by the mass spectrometer and the fir. At first pyrolysis gc was carried out by trapping the effluents and analyzing them by both ir and ms (11,12). Then, as a result of the growth and enhancement of computer hardware throughout the 1970s, the first gc/ir/ms system was demonstrated in 1981 (13).

Instrumental Interface. Gc/ir/ms systems are possible because the infrared technique is nondestructive of sample. Thus several options are available for interfacing the ir and ms instrumental components including both serial and parallel methods. For the serial configuration the gc effluent must first go through the ir flow cell and then into the ms. Parallel methods include utilizing a splitter at the end of the gc column which directs a portion of the effluent to each of the ir and ms instruments. Another parallel approach employs two capillary gc columns in a single injection port such that the effluent of one column is directed into the ir, the effluent of the other into the ms.

Each interfacing technique has certain advantages that depend on the application, but the serial approach is a good first choice because it allows the maximum amount of sample into the ir which generally has a lower sensitivity than the ms. In addition, matching corresponding ir and ms peaks in complex multicomponent chromatograms is more straightforward in serial instruments because each peak in the ms chromatogram (TIC) trails by a few seconds the peak in the ir chromatogram also known as the Gram-Schmidt or total response chromatogram (TRC).

Economic Aspects. Costs for gc/ir/ms instruments vary widely depending on the sophistication of the components. At the lower end of the scale is the flow cell type gc/firs connected to a benchtop mass spectrometer. These are available for about \$115,000–150,000. The isolation type gc/fir can also be interfaced with a benchtop mass spectrometer. The prices range from about \$200,000–300,000.

Applications. The capabilities of a gc/ir/ms in separating and identifying components in complex mixtures is very high for a broad spectrum of analytical problems. One area where ir information particularly complements ms data is in the differentiation of isomeric compounds. An example is in the analysis of tricresyl phosphates (TCPs) used as additives in a variety of products because of their lubricating and antiwear characteristics (see LUBRICATION AND LUBRICANTS). One important use of TCPs is in hydraulic fluid where they tenaciously coat metal surfaces thereby reducing friction and wear. Tricresyl phosphate [1330-78-5], $C_{21}H_{21}O_4P$, exists in a variety of isomeric forms and the commercial product is a complex mixture of these isomers.

Animal feeding studies showed that TCPs containing an ortho-substituted aromatic ring are much more toxic than the other TCP isomers (14). Thus to check for a potential health and safety hazard it was necessary to analyze the TCPs in the hydraulic oil. The gc/ir/ms technique proved very useful. The gc separated the bulk of the oil from the TCPs which appeared as four small peaks late in the chromatogram at a temperature of about 250°C; ms data confirmed that the four small peaks were indeed TCPs as evidenced by a strong molecular ion (M-1) peak at 368 m/z. However, the fragmentation pattern for each of the isomers was nearly identical. The ir data, on the other hand, provided the substitution pattern information given in Figure 3. Ir absorption rules for aromatic substitution clearly identify the TCP isomers present in the hydraulic oil as trimeta (TMCP), metametapara (MMPCP), metapara (MPCP), and tripara (TPCP) without the need for analytical standards. Thus the question of the presence of any of the toxic ortho-isomers was answered clearly, conveniently, and with high confidence using gc/ir/ms.

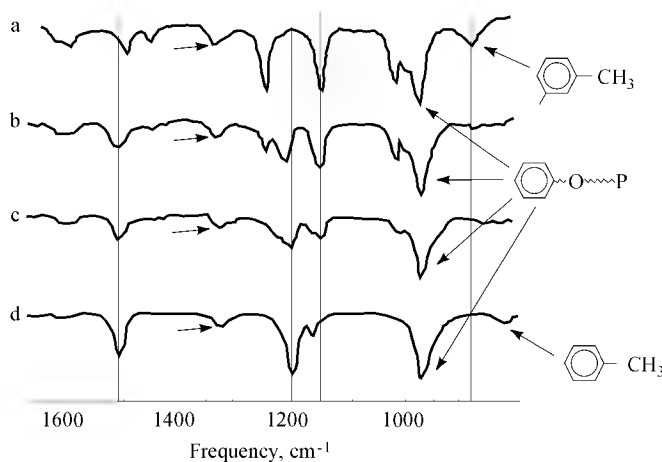


Fig. 3. Infrared absorption data for the four tricresyl phosphate isomers present in hydraulic oil. a, Trimetacresyl phosphate; b, metametaparcresyl phosphate; c, metaparcresyl phosphate; d, triparacresyl phosphate. The P=O stretch between 1300 and 1350 cm^{-1} is marked as is the phenyl-phosphate vibration around 965 cm^{-1} . Also included are the metacresyl (875 cm^{-1}) and paracresyl (820 cm^{-1}) frequencies.

Another analysis handled effectively by use of gc-ir-ms is essential oil characterization which is of interest to the foods, flavors, and fragrances industries (see OILS ESSENTIAL). Even very minor components in these complex mixtures can affect taste and aroma. Figure 4 shows the TRC and TIC for Russian coriander oil which is used extensively in seasonings and perfumes (15). The ir and ms are serially configured. Spectra can be obtained from even the very minor gc peaks representing nanogram quantities in the ir flow cell.

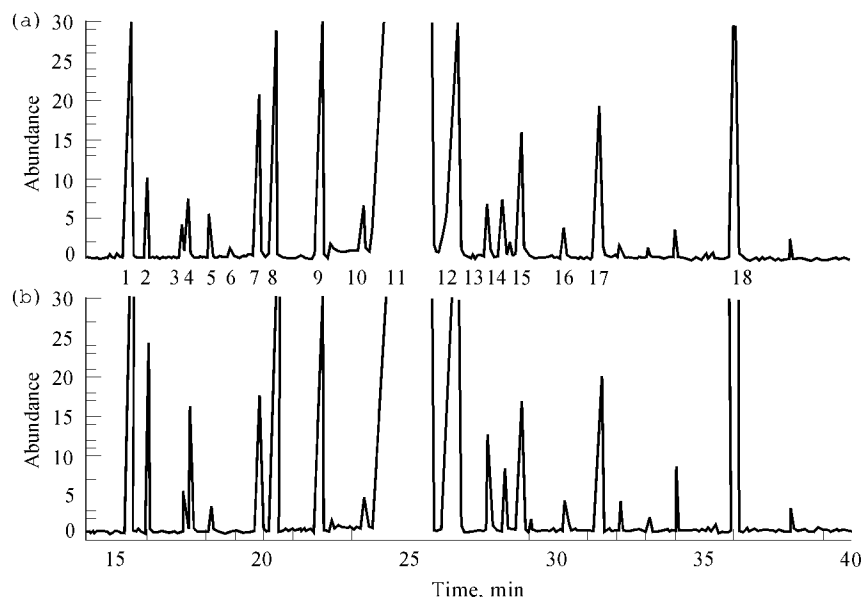


Fig. 4. Chromatograms of Russian coriander oil injected into a serially configured gc-ir-ms: (a) total ion chromatogram (TIC); (b) total response chromatogram (TRC).

The confidence level in the identification capability for gc-ir-ms is enhanced by the ability to perform computer library searching of large spectral databases. Unknown spectra are searched against reference databases and a hit quality number, indicating how well the unknown spectrum matches the library spectra, is generated. For the very small peak at 19 min in Figure 4, peak 6 in the TIC, the library search identified the component as α -phellandrene [99-83-2], $C_{10}H_{16}$, for both the ir and ms data. Because these data are complementary and generated from two completely independent principles of detection, this method provides virtually irrefutable evidence as to a component's correct identity. The complementary nature of the data is further demonstrated by another component in this essential oil. Late in the chromatogram is a long-chain aliphatic alcohol. The mass spectral data confirmed an unsaturated aliphatic chain of specific length, but because of dehydration in the ion source of the ms no alcohol group was evident. On the other hand, the infrared spectrum indicated the presence of an alcohol functionality, but gave little evidence with regard to the length of the aliphatic chain. Thus the combination of complementary ir and ms data was the key to the correct identification of this compound.

Liquid Chromatography/Mass Spectrometry

The replacement of a gas chromatograph with a liquid chromatograph (lc) substantially enhances the separation of compounds which might decompose at the operating temperatures of the gc or which are not readily volatilized. However, lc-ms coupling presents a problem in terms of removing the large quantities of lc solvent. The lc-ms technique had its beginnings as early as 1973–1974 (16–18). In the early stages of lc-ms, there was much debate on whether the combination should be an off-line or on-line process because the quantity, about 1–2 mL min, of solvent is far more than the ms pumping system can handle. Newer instruments utilize direct introduction, on-line techniques.

Instrumental Interfaces. The ideal lc-ms interface should place no compromises on either the lc or the ms. Decomposition or loss of analyte should be avoided and efficient transfer provides for optimum sensitivity.

One direct lc-ms interface is referred to as the particle beam approach based on the Monodisperse Aerosol Generation Interface for lc (MAGIC) (19,20). The MAGIC is actually a rather simple transport device, similar to a two-stage jet separator, where the solvent vapor is pumped away and the analyte particles are concentrated in a beam that is allowed to enter the ms ion source to be vaporized and ionized by electron impact. The particle beam interface consists of four main sections: nebulizer, desolvation chamber, momentum separator, and transfer probe. In the nebulizer the lc effluent is joined by a stream of helium and converted into an aerosol of droplets having a narrow range of diameters. As the droplets move through the desolvation chamber, which is held close to ambient pressure and temperature, the solvent is vaporized creating a mixture of helium, solvent vapor, and analyte particles. As the mixture advances toward the lower pressure, two-stage momentum separator, it is focused into a narrow beam that expands at supersonic speed as it exits the jet nozzle entering the momentum separator. In the separator, the lower mass solvent vapor is pumped and skimmed away while the higher mass, and thus higher momentum, particles pass in a narrow beam through the transfer probe into the ms ion source where they strike the heated source wall and are vaporized.

Another popular type of on-line lc-ms coupling is called the thermospray interface. In contrast to the particle beam approach, thermospray serves as a means for both droplet formation and ionization. The lc effluent first enters the thermospray vaporizer probe where partial vaporization of the liquid occurs to form droplets. As the liquid droplets evaporate and decrease in size, ions present in the droplets are ejected. These ionized molecules then diffuse through a chamber and exit through a small sampling cone into the high vacuum chamber. The ions exit, are directed into the quadrupole analyzer, and are detected in the electron multiplier. This technique provides soft ionization, ie, formation of molecular adduct ions having minimal fragmentation and structural information. Volatile buffers such as ammonium acetate are used to enhance ionization and to provide a reagent for chemical ionization of the analyte. An electric discharge such as a Townsend discharge may be used, if desired, along with an electron filament to create additional fragmentation and to increase sensitivity. Generally, the filament-on mode produces more abundance than the filament-off mode. Temperature control of the vaporizer process is required for optimum sensitivity and reproducibility.

The particle beam and thermospray interfacing techniques are actually complementary in nature. The particle beam approach is the best choice for producing electron impact spectra which can then be library searched against spectral databases. In addition, the particle beam approach is somewhat less complex and easier to use than the thermospray technique. The thermospray approach, which produces chemical ionization spectra, is very useful for high molecular weight compounds that have ion volatility. Because there is very little fragmentation when using the thermospray, selected ion monitoring (sim), where sensitivity is enhanced usually several orders of magnitude over full scan mode, can be effectively used.

Economic Aspects. The lc interface to a mass spectrometer is usually provided as an option to the more sophisticated, full capability instruments. Some systems can have both lc and gc interfaces and can conveniently switch between the two modes. Lc interfaces are approximately \$30,000 bringing a lc-ms that includes a data system into the \$130,000–180,000 range.

Applications. The primary advantage of an lc-ms is in combining the separation of large, potentially thermally labile compounds with the

qualitative and quantitative features of the mass spectrometer. As the need to analyze mixtures containing larger biological molecules increases in the fields of pharmaceuticals (qv), agricultural chemistry, and biotechnology, the demand for lc–ms should also increase.

When the compounds of interest are fragile and thermally labile, thermospray lc–ms is a good choice. Figure 5, shows the thermospray spectrum for leucine enkephalin [58822-25-6], a pentapeptide of molecular weight 555. The lc–ms approach has been very helpful in unraveling the structure of large biological molecules (21).

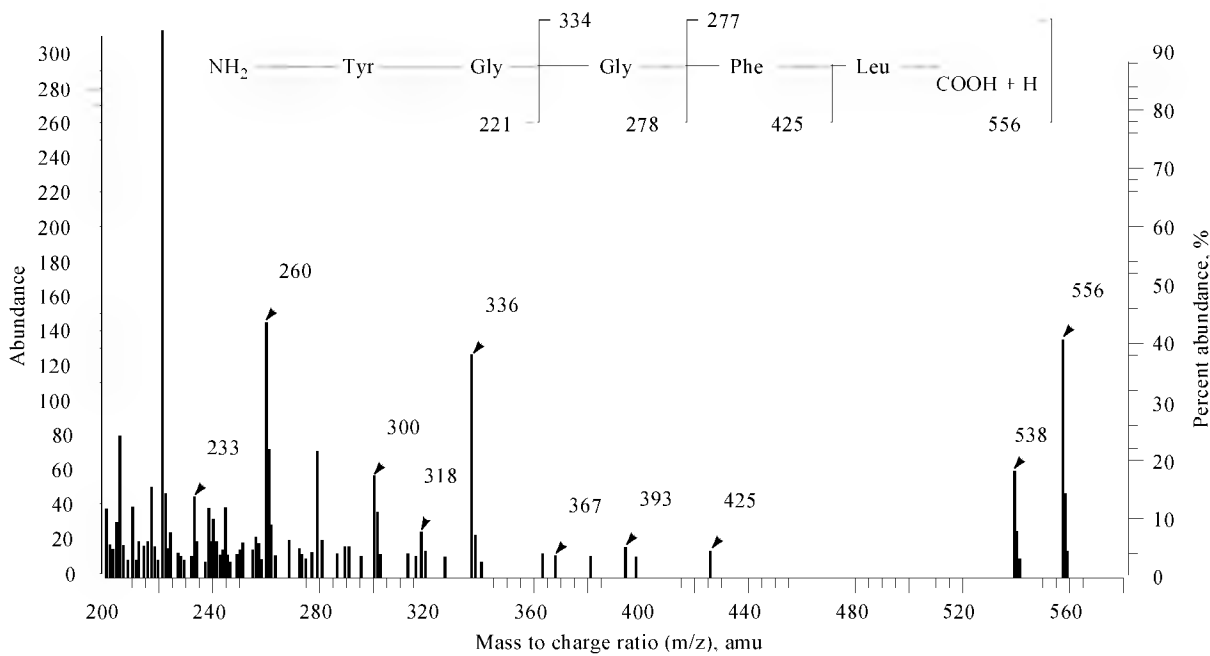


Fig. 5. Thermospray lc–ms analysis of leucine-enkephalin mol wt 555.

Lc–ms has also been effective in environmental analysis. Many compounds designated hazardous that require monitoring are either too heavy or too thermally labile to pass through a gas chromatograph. The polyaromatic hydrocarbons (PAHs), especially those having five or more rings, are an example. Figure 6 shows the particle beam lc–ms analysis of a hazardous waste sample. The compound at about 23 min in the TIC was library searched using a large database of electron impact spectra and found to be benzo[*a*]pyrene [50-32-8], C₂₀H₁₂, mol wt 252.3.

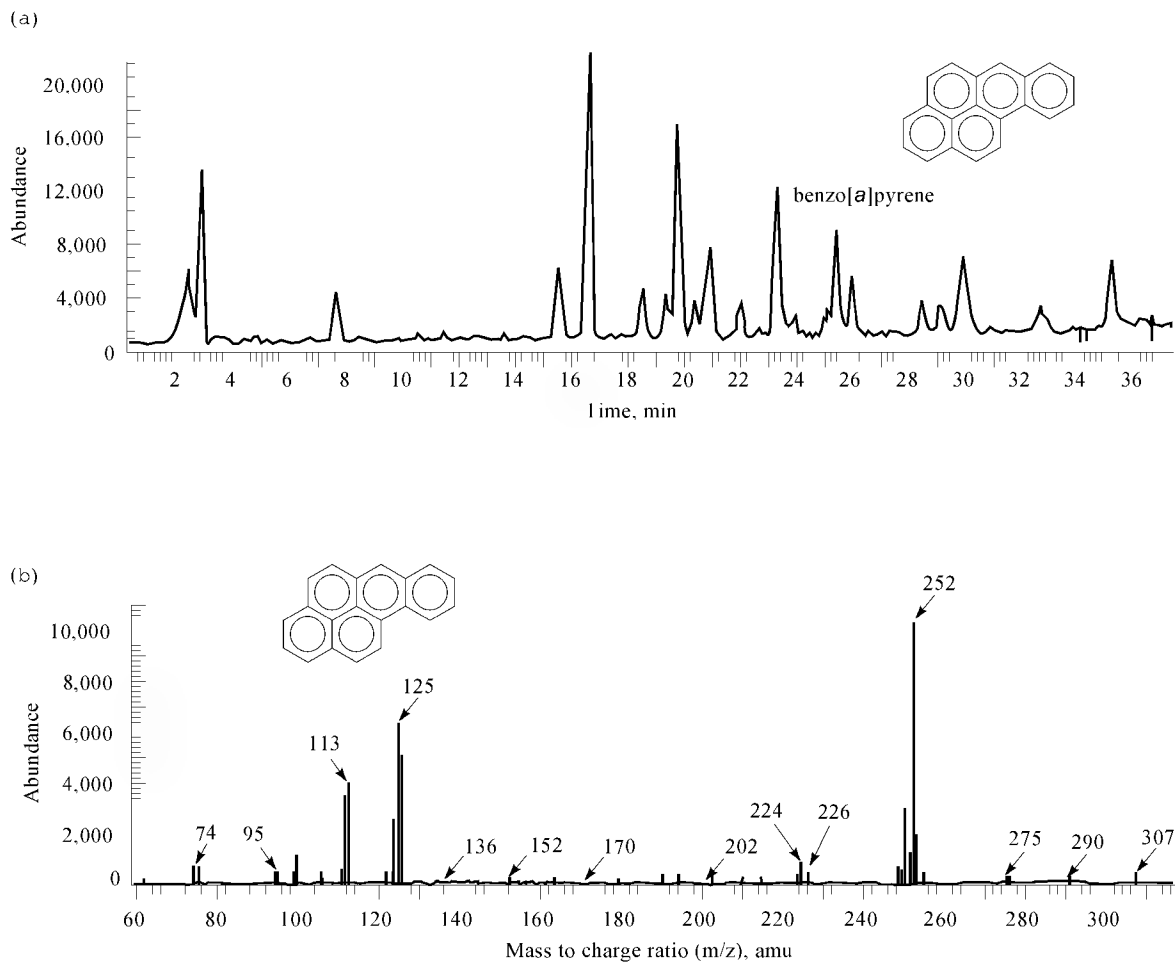


Fig. 6. Particle beam lc–ms analysis of a complex hazardous waste sample (a) TIC showing peak at 23.23 min; (b) mass spectrum of 23.23 min peak of TIC.

Other Techniques. A growing technique related to lc–ms and regarded as complementary to it is that of capillary zone electrophoresis–mass spectrometry (cze–ms) (22). Using cze–ms, high resolution separation of water-soluble compounds is accomplished by the principles of electrophoresis (qv). The sample is then coupled to the mass spectrometer by electrospray ionization (23) or a fast atom bombardment interface (fab) to produce molecular ions (24). Biotechnology applications of cze–ms have great potential (25).

Mass Spectrometry/Mass Spectrometry

Tandem mass spectrometry or ms ms was first introduced in the 1970s and gained rapid acceptance in the analytical community. The technique has been used for structure elucidation of unknowns (26) and has the ability to provide sensitive and selective analysis of complex mixtures with minimal sample clean-up (27). Developments in the mid-1980s advancing the popularity of ms ms included the availability of powerful data systems capable of controlling the ms ms experiment and the viability of soft ionization techniques which essentially yield only molecular ion species.

Ms ms is based on the characterization of selected ions in the mass spectrum of a sample through further fragmentation and analysis. Fragmentation can be spontaneous or induced, although most instruments rely heavily on induced ion dissociations. Collisional activation is the most common approach. The system consists of an ion source, two mass analyzers separated by a fragmentation region, and an ion detector. The principles are straightforward and can be compared to conventional gc ms. A sample mixture is introduced into the ion source where ionization takes place producing ions characteristic of the individual components. The separation of the component of interest is then achieved by the mass selection of a characteristic ion of the analyte by the first mass analyzer. This parent ion undergoes collisionally activated dissociation through collisions with neutral gas molecules in the fragmentation region to yield daughter ions which are analogous to the fragmentation occurring in the initial gc ms ionization step. Identification of the separated components is accomplished by mass analysis of the daughter ions in the second mass analyzer.

The most common modes of operation for ms ms systems include daughter scan, parent ion scan, neutral loss scan, and selected reaction monitoring. The mode chosen depends on the information required. Structural identification is generally obtained using daughter or parent ion scan. The mass analyzers commonly used in tandem systems include quadrupole, magnetic-sector, electric-sector, time-of-flight, and ion cyclotron resonance. Some instruments add a third analyzer such as the triple quadrupole ms (27).

The main advantages of the ms ms systems are related to the sensitivity and selectivity they provide. Two mass analyzers in tandem significantly enhance selectivity. Thus samples in very complex matrices can be characterized quickly with little or no sample clean-up. Direct introduction of samples such as coca leaves or urine into an ms or even a gc lc ms system requires a clean-up step that is not needed in tandem mass spectrometry (28,29). Adding the sensitivity of the electron multiplier to this type of selectivity makes ms ms a powerful analytical tool, indeed. It should be noted that introduction of very complex materials increases the frequency of ion source cleaning compared to single-stage instruments where sample clean-up is done first.

Economic Analysis. Costs of ms ms instrumentation remain at the high end of the scale for hyphenated systems. Because more powerful computer systems are becoming available at lower cost and improvements are being made in the less expensive ms hardware, the trend in instrumental cost is downward. The current range for ms ms systems extends from about \$350,000 to about \$1.4 million where the ms components are equipped with higher mass and resolution capabilities.

Applications. Ms ms has found application in areas such as trace analysis of biological tissue (30), complex hazardous waste site samples (31), and human blood serum (32), as well as in drug testing (33). Anabolic steroids are synthetic derivatives of the male sex hormone testosterone. Although many athletic governing bodies, eg, the International Olympic Committee, have strict rules prohibiting use, these drugs are utilized for both human and equine performance enhancement in sporting events. Routine testing of participants is performed.

One anabolic steroid, the presence of which has proven difficult to analyze, is stanozolol [10418-03-8], C₂₁H₃₂N₂O. A metabolite of the parent drug, hydroxy stanozolol, detected in equine urine eight hours after ingestion of the parent drug is actually identified, usually at very low levels. Analysis was done by lc ms ms which had a shortened analysis time advantage over gc ms procedures because of the elimination of the need for a derivatization step (33).

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ANDROGENS.

See HORMONES.

ANDROSTERONE.

See HORMONES.

ANESTHETICS

The term anesthesia comes from the Greek "anaisthai" or insensibility and constitutes a state in which perception of noxious events such as surgical procedures are imperceptible. This state may or may not be accompanied by loss of consciousness. A complete or general anesthetic given by the inhalation or intravenous route produces hypnosis (profound sleep), analgesia, muscle relaxation, and protection against the increase in blood pressure and heart rate resulting from surgical stress (maintains homeostasis). An anesthetic which blocks the neural transmission of painful stimuli through afferent nerves and does not affect the level of consciousness can be classified as a local anesthetic.

The induction of general anesthesia produces a progressive deepening of the anesthetic state and represents, in the anatomical sense, a descending desensitization of the central nervous system (CNS). A progression of clinical signs are useful for estimating the depth of anesthesia. These signs vary somewhat for each anesthetic, but in general four stages can be defined (1): (1) State of altered consciousness and analgesia indicative of action on cerebral corticulate areas begins. (2) Loss of consciousness, often accompanied by delirium and excitement, occurs. Irregular respiration and motor movement result from depression of higher motor inhibitory centers with the release of lower motor mechanisms. (3) Stage of surgical anesthesia is reached in which spinal cord and spinal reflexes are abolished providing relaxation of skeletal musculature. Within the four planes in this state are loss of corneal, conjunctival, pharyngeal, and laryngeal reflexes as the depth of anesthesia progresses. (4) Onset of respiratory paralysis occurs resulting from significant depression of the medullary respiratory center. Subsequent cardiovascular collapse ensues.

Most signs which require a skeletal muscle reflex would not be apparent after treatment with a neuromuscular blocking drug or would be altered significantly by preoperative drugs. In these cases central nervous system monitoring via an electroencephalogram (EEG), and hemodynamic and blood gas monitoring, help assess the depth of anesthesia. The potency of inhaled agents is expressed as the minimum alveolar concentration (MAC) that is required to prevent spontaneous movement in response to a surgical or equivalent stimulus in 50% of patients (2).

The onset of action is fast (within 60 seconds) for the intravenous anesthetic agents and somewhat slower for inhalation and local anesthetics. The induction time for inhalation agents is a function of the equilibrium established between the alveolar concentration relative to the inspired concentration of the gas. Onset of anesthesia can be enhanced by increasing the inspired concentration to approximately twice the desired alveolar concentration, then reducing the concentration once induction is achieved (3). The onset of local anesthetic action is influenced by the site, route, dosage (volume and concentration), and pH at the injection site.

Theories of General Anesthesia

Although the modern practice of anesthesia is exceedingly sophisticated, the basic molecular mechanism underlying it is still lacking. Even whether the target sites of the inhalational anesthetics are lipid or protein remains unknown, although it is likely that proteins are intimately involved. The inhalational anesthetics are very diverse chemically and extrapolation from the effect of a particular agent to the physiological state of anesthesia is problematic. However, anesthesia theories may be roughly divided into two categories: lipid theories and protein theories (4–6).

Lipid Theories. Although there are many varieties of the lipid theory, all postulate that inhalational anesthetics exert their primary effects by dissolving in the lipid portions of nerves thereby altering the conductivity. This theory is based on observations made at the turn of the twentieth century on the relationship between anesthetic potency and the partition coefficient of the agent between olive oil and gas (7–9). The anesthetic potency of a wide variety of anesthetics, covering four orders of magnitude, correlates exceedingly well with the agent's oil-gas partition coefficient.

The primary site of action is postulated to be the lipid matrix of cell membranes. The lipid properties which are said to be altered vary from theory to theory and include: enhancing membrane fluidity; volume expansion; melting of gel phases; increasing membrane thickness, surface tension, and lateral surface pressure; and encouraging the formation of polar dislocations (10,11). Most theories postulate that changes in the lipids influence the activities of crucial membrane proteins such as ion channels. The lipid theories suffer from an important drawback: at clinically used concentrations, the effects of inhalational anesthetics on lipid bilayers are very small and essentially undetectable (6,12,13).

Protein Theories. The direct interaction of inhalation anesthetics and proteins (qv) has been proposed as the cause of anesthesia (12,14). An inhalation agent, whether a noble gas or a fluorinated ether, could dissolve asymmetrically in a protein (6,15). Resultant conformational changes in the protein, if these changes occur, could then cause changes in activity, for example, the chloride ion channel which is modulated by many of the intravenous agents. Quantitative data on the binding of anesthetics to proteins are limited but are related to anesthetic partition coefficients (16,17). Although binding to a soluble protein and modulation of its function are not necessarily coupled (18,19), the proteins of interest are those involved in nerve impulse transmission and are embedded in lipid membranes. Thus dissociation of lipid and protein effects is not possible.

The membrane enzyme luciferase, responsible for light emission in fireflies, is sensitive to anesthetics (20,21), and the concentrations of inhalational agents which inhibit luciferase are the same as those which cause general anesthesia. Studies of various classes of inhalational agents and luciferase demonstrated that above a certain chain length in a homologous series, a point is reached where higher members are not anesthetic. The same cut-off effect in efficacy is observed in anesthesia (22). This effect is not explainable by lipid theory.

Anesthetic Agents

INHALATION AGENTS

An ideal inhalation anesthetic would exhibit physical, chemical, and pharmacological properties allowing safe usage in a variety of surgical interventions. The agent should be odorless, nonflammable at concentrations which are likely to be used in the operating room, and stable both on storage and to soda lime, which is used as the CO₂ absorber in the anesthetic circuit. Induction of, and recovery from, anesthesia should be rapid, and minimal side effects

should be observed on the cardiovascular (depression and epinephrine compatibility) or central nervous systems (EEG activation) (see EPINEPHRINE AND NOREPINEPHRINE; NEUROREGULATORS). The drug should not be metabolized.

A number of inhalation anesthetics have been introduced to clinical practice, some of which are listed in Table 1. All agents introduced after 1950, except ethyl vinyl ether, contain fluorine. Agents such as ether, chloroform, trichloroethylene (Trilene), cyclopropane, and fluoroxene (Fluoromar), which were once used, have been displaced by the newer fluorinated anesthetics.

Table 1. Properties and Partition Coefficients of Inhalation Anesthetics

Agent	CAS Registry Number	Molecular formula	Partition coefficients ^a		Boiling point, °C	Year introduced
			Oil gas	Blood gas		
ethyl ether	[60-29-7]	C ₄ H ₁₀ O	65	12.1	35	1842
chloroform	[67-66-3]	CHCl ₃	394	8.4	61	1847
trichloroethylene	[79-01-6]	C ₂ HCl ₃	200–250	9.0	87	1934
fluoroxene	[406-90-6]	C ₄ H ₅ F ₃ O	47	1.37	43.1	1960
halothane	[151-67-7]	C ₂ HBrClF ₃	224	2.3	50.2	1956
isoflurane	[26675-46-7]	C ₃ H ₂ ClF ₅ O	90.8	1.4	48.5	1980
enflurane	[13838-16-9]	₃ H ₂ ClF ₅ O	96.5	1.9	56.5	1972
methoxyflurane	[76-38-0]	C ₃ H ₄ Cl ₂ F ₂ O	970	12.0	105	1962
sevoflurane	[28523-86-6]	C ₄ H ₃ F ₇ O	42	0.6	58	1989
desflurane	[57041-67-5]	C ₃ H ₂ F O	18.7	0.42	23.5	
nitrous oxide	[10024-97-2]	N ₂ O	1.4	0.46	89.5	1850s
cyclopropane	[75-19-4]	C ₃ H			33	1934

^a Ref. 23.

Historical Inhalation Agents. Diethyl ether produces excellent surgical anesthesia, but it is flammable (see ETHERS). Chloroform is a nonflammable, sweet smelling, colorless liquid which provides analgesia at nonanesthetic doses and can provide potent anesthesia at 1° (see CHLOROCARBONS AND CHLOROHYDROCARBONS). However, a metabolite causes hepatic cell necrosis. Trilene, a nonflammable colorless liquid, has a slower onset and recovery and a higher toxicity and chemical reactivity than desirable. Cyclopropane is a colodess gas which has rapid induction (2–3 min) and recovery characteristics and analgesia is obtained in the range of 3–5° with adequate skeletal muscle relaxation (see HYDROCARBONS). The use of cyclopropane has ceased, however, because of its flammability and marked predisposition to cause arrhythmias.

Because of the flammable nature of diethyl ether and cyclopropane, a number of hybrid molecules were prepared in an attempt to improve on the useful characteristics of each, but none were marketed (24,25). Structure activity relationships for halogenated hydrocarbons and ethers (26) indicated that fluorine (qv) was the most suitable halogen to use in order to decrease the potential for cardiac arrhythmias. In addition, the introduction of fluorine decreases flammability and boiling point and increases stability (see FLUORINE COMPOUNDS, ORGANIC). It also decreases anesthetic potency. Fluoroxene, 2,2,2-trifluoroethyl vinyl ether [406-90-6], the first fluorinated ether prepared and commercialized (27), has oil gas and blood gas partition coefficients (Table 1) lower than ether, chloroform, or Trilene, contributing to a rapid onset and recovery. This agent is less potent (MAC = 3.4%) than other fluorinated hydrocarbons introduced later and its flammability is close to MAC. Whereas the agent is stable to soda lime, it is readily oxidized and hydrolyzed to trifluoroethanol and acetaldehyde and is unstable to light (28). Fluoroxene is also metabolized to a significant extent (29,30). Thus it is no longer used.

Clinical Inhalation Agents.

Nitrous Oxide. Nitrous oxide, described by Priestly in 1772, was first used to relieve severe dental pain in the latter part of the 18th century. Sometime in the mid-1800s N₂O was successfully used as an anesthetic, and its widespread usage coincided with the development of anesthesia machines. Nitrous oxide is a nonflammable, colorless, odorless, and tasteless gas that can exist as a liquid under pressure at room temperature. It is normally stored in cylinders. However, it supports combustion.

A mixture of 20° nitrous oxide and 80° oxygen produces analgesia equivalent to 15 mg of morphine in humans (see ANALGESICS, ANTIPYRETICS, AND ANTIINFLAMMATORY AGENTS) (31,32). Effects of nitrous oxide can be partially reversed using opiate antagonists and it has been suggested that the agent interacts with endogenous opioids (23,33,34) (see OPIOIDS, ENDOGENOUS). Because of analgesic properties, N₂O is added to other inhaled anesthetics and to opioids at concentrations usually between 30 and 70° in oxygen. Nitrous oxide is a very weak anesthetic, MAC = 104%. However, the blood gas partition coefficient has been established to be about 0.46 (35,36) allowing the agent to come into rapid equilibrium with the inspired and alveolar concentrations (37). Because of poor solubility in blood and other tissues, induction and recovery from nitrous oxide administration is rapid.

Nitrous oxide produces respiratory depression (38,39). It has been shown to produce a direct myocardial depressant effect in dogs (40) and in humans breathing a 40° N₂O 60° oxygen mixture (41); however, this may be offset by the activation of the sympathetic nervous system (42). The combination of nitrous oxide and opioids can produce decreases in myocardial contractility, heart rate, and blood pressure (43).

There appear also to be toxic effects. In animals, nitrous oxide has been shown to inactivate methionine synthetase which prevents the conversion of deoxyuridine to thymidine and thus has the potential for inducing megaloblastic anemia, leukopenia, and teratogenicity (44–46). A variety of epidemiologic surveys suggest positive correlations between exposure to nitrous oxide and spontaneous abortion in dental assistants (47).

Methoxyflurane. Methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether) [76-38-0], a clear colorless liquid having a vapor pressure of 2.70 kPa (20.3 mm Hg) at 20°C, is not irritating to the respiratory tract. Its odor has been described as sweet or fruity. Whereas the odor may make this agent suitable for inhalation induction, the blood gas and oil gas partition coefficients (Table 1) are very high and thus onset and recovery are the slowest of all anesthetics (48). Methoxyflurane is stable to light and soda lime, but not to oxygen; it is nonflammable and nonexplosive at anesthetic concentrations (28). Methoxyflurane is the most potent of the inhaled anesthetics having MAC = 0.6%. The agent is both a respiratory and cardiovascular depressant (49). It also produces muscle relaxation as the depth of anesthesia increases.

Approximately 50° of an absorbed dose is transformed to fluoride ion, dichloroacetic acid, methoxydifluoroacetic acid, and oxalic acid (50). Because of fluoride ion associated renal impairment, the duration of anesthesia using methoxyflurane must be limited (51,52).

Halothane. Halothane or Fluothane, 2-bromo-2-chloro-1,1,1-trifluoroethane [151-67-7], is a colorless liquid with a pleasant odor. Its lower flammability limit, 4.8° in 70° N₂O 30° O₂, renders it essentially nonflammable. It has a vapor pressure of 32.5 kPa (244 mm Hg) at 20 °C and is stable to soda lime. However, it is photochemically reactive.

Halothane is a potent anesthetic having a MAC value of 0.77°. MAC requirements, as in other inhaled anesthetics, increase in younger patients and decrease in the elderly (53). Halothane is a cardio-respiratory depressant which produces changes in cardiac output and arterial pressure comparable to the other inhalation agents, isoflurane or enflurane. Halothane does not decrease peripheral vascular resistance as do these others. It is also the least likely of the inhalants to cause an increase in heart rate. The ability of halothane to sensitize the heart to arrhythmogenic effects of epinephrine is the greatest of the inhalants (54), although halothane produces less muscle relaxation than isoflurane (55). Approximately 20° of an absorbed dose of halothane is oxidatively metabolized to trifluoroacetic acid (56,57) and halothane has been implicated in producing liver dysfunction in a very small number of patients (58).

Fluoride produced from the biodegradation of halothane or the other agents has little effect on normal kidney function (59). Halothane usage has been declining because of the potential liver effects, although the agent is used where inhalation induction is desired, especially in pediatrics.

Enflurane. Enflurane or Ethrane, 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether[13838-16-9], was synthesized in 1963. This agent is a mildly pungent colorless liquid having a vapor pressure of 22.85 kPa (171.8 mm Hg) at 20°C. Enflurane is stable to soda lime and light (28). The minimum flammable concentration is 5.8° in 70° N₂O 30° O₂, placing its flammability between that of halothane and isoflurane. Enflurane is the least potent of the inhaled anesthetics marketed in 1990. It has a MAC value of 1.7° (60), although the solubility characteristics of enflurane are similar to those of isoflurane and halothane (Table 1) and recovery is both rapid and less complicated by nausea than in the case of halothane (61–63).

When compared with isoflurane and halothane at equi-anesthetic concentrations, enflurane produces a greater degree of respiratory depression (64). Hemodynamic parameters such as cardiac output, stroke volume, and blood pressure decrease where heart rate is only slightly changed. Surgical stimulation tends to reverse depressed cardiac output and arterial blood pressure (65). In the presence of epinephrine, enflurane does not potentiate arrhythmias to the same extent as halothane (66). Enflurane provides muscle relaxation and when combined with neuromuscular blocking drugs, the block is enhanced, allowing lower doses of the relaxant to be used (67,68). Unlike other inhalational anesthetics, enflurane at high concentrations causes EEG changes which are seizurelike. Enflurane is oxidatively metabolized in the liver. In humans, about 2.4° of the enflurane is metabolized (69), but clinically significant hepatic dysfunction is rare.

Isoflurane. Isoflurane or Forane, 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether [26675-46-7], was prepared in 1965 (28). It is a clear, colorless liquid having a vapor pressure of 31.85 kPa (239.5 mm Hg) at 20°C. It has an ethereal odor which may limit the rate at which the inspired concentration may be increased for a rapid induction. The agent is stable to soda lime and light, and does not react with metals. The minimum flammable concentration is 7° in 70° N₂O 30° O₂. Isoflurane is a potent anesthetic having a MAC value of 1.15° in O₂ (70). MAC requirements are decreased by increasing age, decreasing body temperature, pregnancy, and a variety of depressant drugs. This agent is the least soluble of the modern volatile agents (Table 1) allowing for a rapid onset and recovery.

Isoflurane is a respiratory depressant (71). At concentrations which are associated with surgical levels of anesthesia, there is little or no depression of myocardial function. In experimental animals, isoflurane is the safest of the oral clinical agents (72). Cardiac output is maintained despite a decrease in stroke volume. This is usually because of an increase in heart rate. The decrease in blood pressure can be used to produce "deliberate hypotension" necessary for some intracranial procedures (73). This agent produces less sensitization of the human heart to epinephrine relative to the other inhaled anesthetics. Isoflurane potentiates the action of neuromuscular blockers and when used alone can produce sufficient muscle relaxation (74). Of all the inhaled agents currently in use, isoflurane is metabolized to the least extent (75). Unlike halothane, isoflurane does not appear to produce liver injury and unlike methoxyflurane, isoflurane is not associated with renal toxicity.

Isoflurane is the most widely used inhalational anesthetic and more closely approaches the ideal than other marketed drugs. It has found application in the anesthetic management of all types of surgical procedures.

Developmental Inhalational Agents.

Sevoflurane. Sevoflurane, 1,1,1,3,3,3-hexafluoro-2-propyl fluoromethyl ether [28523-86-6], is nonpungent, suggesting use in induction of anesthesia. The blood gas partition coefficient is less than other marketed products (Table 1) yet similar to nitrous oxide, suggesting fast onset and recovery. In animal studies, recovery was faster for sevoflurane than for isoflurane, enflurane, or halothane (76). Sevoflurane is stable to light, oxygen, and metals (28). However, the agent does degrade in soda lime (77).

Sevoflurane is less potent than clinically used inhalation agents having MAC of 1.71° and 2.05° in humans (78,79). Sevoflurane is also a respiratory depressant similar to other agents (78,80) decreasing both blood pressure and heart rate (80). Sevoflurane decreases myocardial oxygen blood flow (81) and the potential to sensitize the myocardium to epinephrine induced arrhythmias is similar to isoflurane (82). Other positive characteristics include sufficient muscle relaxation and an EEG pattern which is devoid of convulsant activity (78,79). Sevoflurane appears to have advantages over current products, especially in regard to onset, recovery, and no increase in heart rate. The primary disadvantage appears to be its instability to soda lime. The drug was launched in Japan in late 1989.

Desflurane. Suprane or desflurane, 1,2,2,2-tetrafluoroethyl difluoromethyl ether [57041-67-5], has a structure similar to isoflurane except for the substitution of a fluorine for the chlorine on the alpha methyl carbon. The agent has a vapor pressure of 88.3 kPa (664 mm Hg) at 20°C. The partition coefficients for blood gas and tissue gas (Table 1) suggest that this agent should have a faster onset and recovery than current agents including sevoflurane (76,83). Its odor is milder than isoflurane when used for induction. In unpremedicated patients upper airway tolerance was good: only transient coughing and easily managed secretions were observed. Desflurane is stable to O₂, light, and metals, and also to soda lime in systems where sevoflurane, halothane, and isoflurane are forced to degrade (84).

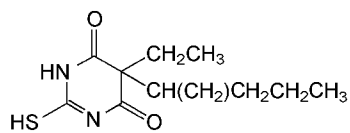
Desflurane is less potent than the other fluorinated anesthetics having MAC values of 5.7 to 8.9° in animals (76,85), and 6° to 7.25° in surgical patients. The respiratory effects are similar to isoflurane. Heart rate is somewhat increased and blood pressure decreased with increasing concentrations. Cardiac output remains fairly stable. Desflurane does not sensitize the myocardium to epinephrine relative to isoflurane (86). EEG effects are similar to isoflurane and muscle relaxation is satisfactory (87). Desflurane is not metabolized to any significant extent (88,89) as levels of fluoride ion in the serum and urine are not increased even after prolonged exposure. Desflurane appears to offer advantages over sevoflurane and other inhaled anesthetics because of its limited solubility in blood and other tissues. It is the least metabolized of current agents.

INTRAVENOUS ANESTHETIC AGENTS

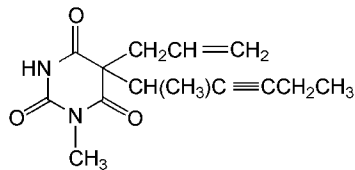
The intravenous (iv) anesthetic agents are of two types: those which are used to induce, but not maintain, anesthesia, and those which are useful not only for induction, but also for maintenance. The period of induction is perhaps the most crucial part of the anesthesia. The need is for an anesthetic agent having an extremely fast rate of onset and limited side effects. Fast onset minimizes the stress and agitation which could arise during a more lengthy induction. An ideal maintenance iv anesthetic has been a goal for over a century. Various classes of compounds have been used. Among these are: barbiturates, opioids, and hindered phenols. But the ideal agent for both induction and maintenance has not yet been found. For this reason, balanced anesthesia is often used: a potent opioid is combined with an inhalational agent.

A major difference between the inhalational agents and the iv anesthetics is that the former probably exert their biological activity through physical effects while the latter, in most cases, function through a biological receptor mediated pathway. There are two primary biochemical receptors used for iv anesthesia in the CNS, the gabaergic (90) and the opiate (91). The γ-aminobutyric acid [56-12-2] (GABA) receptor controls a chloride ion channel and the GABA receptor itself is modulated by various drug receptors for the barbiturates, anesthetic steroids, and benzodiazepines. An increase in GABA binding results in a variety of effects: anesthesia, sleep, amnesia, muscle relaxation, and an antianxiety effect. The opiate receptor, of which there are various types, controls analgesia (92). Its primary endogenous ligands are the enkephalins and endorphins. However, the more familiar plant alkaloid morphine [57-27-2] also binds strongly to this receptor (93). Because anesthesia using iv agents is receptor based, antagonists have been developed which can reverse the activity of these anesthetics.

Barbiturates. The first class of readily accepted iv anesthetics were barbiturates. This group's biological activity results from interaction with a drug receptor that modulates GABA binding (94,95). The first of these agents was thiopental [76-75-5] (Pentothal) C₁₁H₁₈N₂O₂S, (1) which is still the most widely used drug for induction. Thiopentone is an ultra short-acting depressant for the CNS which induces hypnosis and amnesia, but not analgesia, within one ambrain circulation time (30–40 s) (96). Its action is predictable, induction is smooth, and recovery after a small dose is rapid, accompanied by some somnolence and retrograde amnesia. The agent does, however, cause respiratory and cardiovascular depression and it accumulates as a result of redistribution into the fatty tissues, so repeated doses are not advisable (97). A general problem with thiobarbiturates is a poor therapeutic index. There is continued research into safer, more effective iv anesthetics (98).



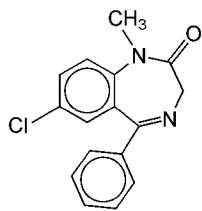
(1)



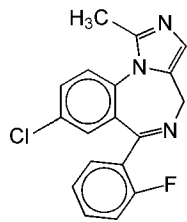
(2)

Methohexital [18652-93-2] (Brevital), C₁₄H₁₈N₂O₃, (2) is a barbiturate iv anesthetic induction agent that has a slightly faster onset than thiopentone and less accumulation. The recovery from anesthesia is also slightly faster and better. However, induction is associated with an increased incidence of excitatory phenomena. Methohexital also causes respiratory and cardiovascular depression and is unstable in solution, necessitating reconstitution before use (99).

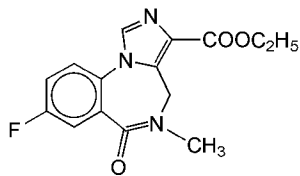
Benzodiazepines. Librium and Valium were first introduced for their muscle relaxant activity, but became widely used for their antianxiety (minor tranquilizer) activity. The benzodiazepines bind to a drug receptor which modulates the binding of GABA to its receptor (100). Diazepam [439-14-5] (Valium), C₁₆H₁₃ClN₂O, (3) is used as a premedicant to anesthesia to lessen preoperative anxiety and to prevent recall of the operative procedure. Midazolam [59467-70-8] (Versed) C₁₆H₁₃ClFN₃, (4) a water soluble benzodiazepine having a shorter duration of action than diazepam (101), has specific applications in anesthesia. Its primary intramuscular use is as a premedicant similar to diazepam. As an iv anesthetic it is comparable to thiopentone for induction but has a slower onset, approximately 1.5 min after opioid premedication and 2–2.5 min without. Recovery is slower using midazolam than it is using thiopentone.



(3)



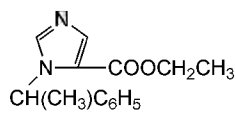
(4)



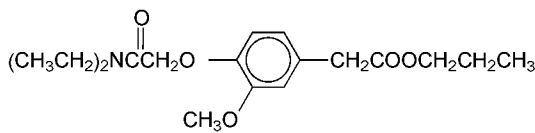
(5)

Midazolam and diazepam decrease arterial pressure without a change in heart rate. Like thiopentone, midazolam is a respiratory depressant. Advantages of midazolam are its amnestic effect, coupled with less postoperative depression (102). A reversal agent for the benzodiazepines has also become available. Flumazenil [78755-81-4], C₁₅H₁₄FN₃O, (5) displaces the benzodiazepines from their receptor but has little demonstrable activity of its own (103,104).

Etomidate. Etomidate [33125-97-2] (Hypnomidate, Amidate), C₁₄H₁₇N₂O₂, (6) is a relatively simple imidazole carboxylic ester developed in the 1970s as an iv anesthetic that became available in the United States in the mid-1980s (105). Etomidate has almost as rapid an onset and short duration of action as thiopentone, but it is approximately twelve times as potent. In contrast to other agents, it is rapidly and extensively metabolized by liver and plasma esterases. It causes less respiratory and cardiovascular depression than thiopentone and does not release histamine. In addition to pain on injection, there is frequent occurrence of extraneous muscle movement (myoclonus), controllable by benzodiazepine or opiate premedication (106). There is also a relatively high frequency of nausea and vomiting, particularly when opiate premedication is used. Despite these disadvantages, etomidate is extensively used in neuro and cardiovascular surgery (107).



(6)



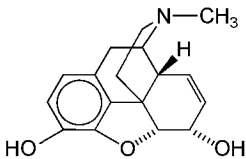
(7)

Propanidid. Propanidid [1421-14-3] (Epontol), C₁₈H₂₇NO₃, (7) a derivative of the propyl ester of homovanillic acid, has been in clinical use in Europe for a number of years. Its main advantage is rapid onset of action and a fast recovery which, like etomidate, is because of rapid metabolism by esterases rather than redistribution (108). Excretion is rapid: 75 to 90% of the drug is eliminated as metabolites within two hours. Propanidid side effects include hypotension, tachycardia, and hyperventilation followed by apnea, as well as excitatory side effects such as tremor and involuntary muscle movement (109).

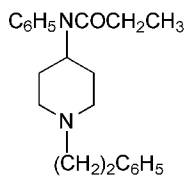
Propofol. 2,6-Diisopropylphenol [2078-54-8], propofol, C₁₂H₁₈O, is a newer intravenous anesthetic used for both induction and maintenance (110). This drug, also known as Diprivan, is chemically unlike any of the previously described iv agents and was developed following the discovery of the anesthetic activity of the 2,6-diethyl analogue (111). Propofol itself is insoluble in water and is usually formulated in a soya bean oil emulsion. Propofol induction, with or without an opioid, is smooth and similar to that of other agents, although pain at the injection site and apnea have been reported (112,113). Recovery after induction and maintenance is faster, with fewer side effects, than with thiopentone (114), although sexual disinhibition has been anecdotally reported (115). Propofol is rapidly distributed, metabolized, and eliminated (116).

Opioids. Morphine [57-27-2], C₁₇H₁₉NO₃, (8) the most prevalent and analgesically potent of the naturally occurring opium alkaloids (qv), has been used as an anesthetic premedication for over one hundred years (93). It has also been used as an iv analgesic for the last four decades, and, since 1969, in high doses as an anesthetic agent (117).

Morphine has certain undesirable side effects. Among these are respiratory depression, nausea, and vomiting, depression of the cough reflex, cardiovascular depression and hypotension, smooth muscle contraction (constipation), and histamine release (93). Morphine's onset of action, duration, and low therapeutic indices have prompted a search for a more effective opiate iv anesthetic. Extreme simplification of the complex morphine molecule has resulted in anilido-piperidines, the fentanyl class of extremely potent opiate iv anesthetics (118,119).

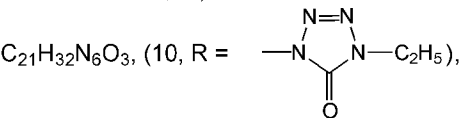


(8)



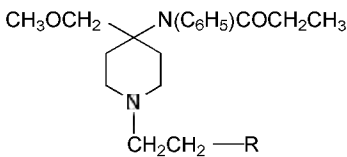
(9)

Fentanyl [437-38-7] (Sublimaze, Leptanal), C₂₂H₂₈N₂O, (9) has been extensively used since its introduction into clinical practice in the 1960s (119). Because of its potency, which is 50–100 times that of morphine, a rapid onset of action and a short duration, its use as an iv anesthetic is widespread. The short duration results from redistribution from the brain to other tissues, rather than elimination. It does, however, have the usual opiate disadvantages; respiratory depression, chest wall rigidity, nausea, and bradycardia. Fentanyl has an extremely wide therapeutic ratio. The size of the dose influences its duration of action which, after iv administration, may last from approximately 30 min to 2 to 3 h (120,121). In cardiac surgery fentanyl is administered in very large doses to produce profound analgesia and suppress cardiovascular reflex responses. This technique is particularly useful for patients with compromised circulation where any increase in cardiac demand could precipitate myocardial ischemia (122).

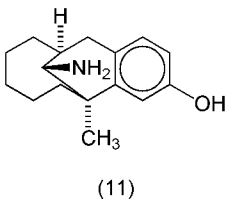


Approved for clinical use in 1986, alfentanil [71195-58-9] (Alfenta, Rapifen), is about one fourth as potent as fentanyl and has a rapid onset. Alfentanil has an extremely short duration of action, from 0.2–0.3 times that of fentanyl (123,124), paralleling its rapid elimination. Thus alfentanil has been given by infusion pumps. Although alfentanil has the usual opiate side effects, its rapid elimination leads to a more rapid recovery and less frequent side effects and complications (125,126).

Sufentanil [56030-54-7] (Sufenta), C₂₂H₃₀N₂O₂S, (10, R = ) is five to ten times as potent as fentanyl. Sufentanil also has a short duration of action, but has an extremely high therapeutic ratio (127). Sufentanil, with less respiratory depression than either alfentanil or fentanyl, is used in high dose opioid anesthesia for cardiac surgery, and as a low dose supplement in balanced anesthesia for general and outpatient surgery (128,129).



(10)



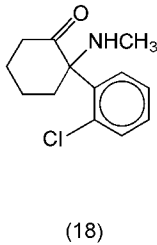
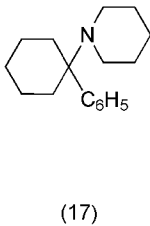
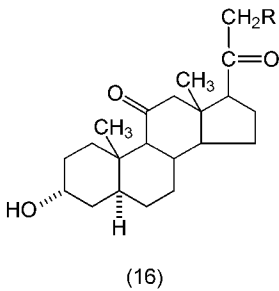
Dezocine [53648-55-8] (Dalgan), C₁ H₂₃NO, (11) is an opiate having both agonist and antagonist properties which lowers MAC requirements for cyclopropane with a ceiling effect on respiratory depression in rats (130) and reduces the MAC requirement for enflurane in dogs (131). Dezocine was effective against post operative pain, producing sedation as a primary side effect (132). The compound has also produced respiratory depression in volunteers but was reported to have a ceiling effect (133,134), and there has been a suggestion of psychotomimetic effects (134).

Opioid Reversal Agents. At the end of a surgery, when the decision is made to reverse opioid induced activity, the primary concern is to eliminate the respiratory depressant effects inherent in the potent opiates used as anesthetics. This reversal, brought about by opioid reversal agents (Table 2), can also diminish the analgesic effects of the opiates. There are two types of reversal agents: pure antagonists and mixed agonist–antagonists. Antagonism of the opiate agonist effect may be viewed as lowering agonist activity below a series of thresholds. The dose can be titrated so that a significant degree of analgesia can remain even though clinically significant respiratory depression is reversed. The antagonists naloxone (12, R = C₃H₇) and naltrexone (12, R = C₄H₇) are the most commonly used, although the use of the agonist–antagonist nalbuphine (15, R = C₄H₇) is increasing because it maintains a moderate level of analgesia while reversing the side effects (143). Nalmefene (13), a long acting reversal agent, is in clinical trials (144). The agonist–antagonist nalorphine (Lethidrone) (15, R = C₂H₅) is not available in the United States. Levallorphan (14) is little used because of nalorphinelike psychotomimetic effects.

Table 2. Opioid Reversal Agents

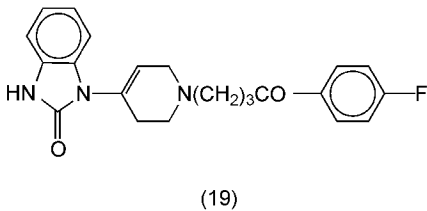
Compound name	CAS Registry Number	Trade name	Molecular formula	Structure number	Structure	Reference
<i>Antagonists</i>						
naloxone	[465-65-6]	Narcan	C ₁₉ H ₂₁ NO	(12, R = CH ₂ CH = CH ₂)		135
naltrexone	[16590-41-3]	Trexan	C ₂₀ H ₂₃ NO	(12, R = CH ₂ — )		136–138
nalmefene	[55096-26-9]		C ₂₁ H ₂₅ NO	(13)		144
<i>Agonist–antagonists</i>						
levallorphan	[152-02-3]	Lorfan	C ₁₉ H ₂₅ NO	(14)		139
nalorphine	[62-67-9]	Lethidrone	C ₁₉ H ₂₁ NO	(15, R = CH = CH ₂)		140,141
nalbuphine	[20594-83-6]	Nubain	C ₂₁ H ₂₇ NO	(15, R = — )		142,143

Steroid Anesthetics. The anesthetic properties of a number of steroids were discovered in 1941 (145) and Althesin, a mixture of alfaxalone [23930-19-0], C₂₁H₃₂O₃, (16, R = H), and alfadone acetate [23930-37-2], C₂₃H₃₄O₅, (16, R = OCH₃), was introduced in 1971 (146). *Althesin* appeared to have many of the ideal iv anesthetic properties. However, it was associated with a high incidence of allergic reactions and implicated in the development of renal failure (147); it was withdrawn in 1984. Like the barbiturates and benzodiazepines, the anesthetic steroids bind to a drug receptor which modulates GABA control of a chloride ion channel (148,149).



Other Anesthetic Agents. Dissociative anesthesia is so called because of the feeling of dissociation engendered by administration of drugs related to phencyclidine [77-10-1] (PCP), C₁₇H₂₅N, (17). The anesthesia, different from that produced by the inhalational and other iv agents, is characterized by a trancelike cataleptic state. However, the eyes can remain open and light reflexes are retained. Ketamine [6740-88-1] (Ketalar), C₁₃H₁₇ClNO, (18) is chemically related to phencyclidine (150). Ketamine anesthesia is characterized by rapid onset but slow recovery, a profound analgesia, and a lack of clinical cardiovascular depression. Unlike other iv agents, it can also be administered intramuscularly. Its greatest disadvantage is that, like PCP, it is a potent psychotomimetic. For this reason, it is only used for trauma patients, asthmatics, children, and patients at high risk (151).

Neuroleptic analgesia is so called because the combination of a major tranquilizer, a neuroleptic drug, and a potent opiate produces an anesthetic state characterized by sedation, apathy, and mental detachment (see PSYCHOPHARMACOLOGICAL AGENTS) (152). Innovar [8067-59-2], a combination of droperidol [548-72-2], C₂₂H₂₂FN₃O₂, (19) and fentanyl (9) citrate, is used for procedures that do not require muscle relaxation. However, the onset of action is slow.



LOCAL ANESTHETICS

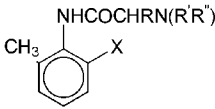
Local anesthetics produce anesthesia by blocking nerve impulse conduction in sensory, as well as motor nerve, fibers. Nerve impulses are initiated by membrane depolarization, effected by the opening of a sodium ion channel and an influx of sodium ions. Local anesthetics act by inhibiting the channel's opening; they bind to a receptor located in the channel's interior. The degree of blockage on an isolated nerve depends not only on the amount of drug, but also on the rate of nerve stimulation (153–156).

Local anesthetic activity is usually demonstrated by compounds which possess both an aromatic and an amine moiety separated by a lipophilic hydrocarbon chain and a polar group (153,157). A selection of local anesthetic agents is given in Table 3. In the clinically useful agents, the polar group is an ester (20) or an amide (21). Activity may be maintained, however, when the polar function is an ether, thioether, ketone, or thioester. The amino esters, more susceptible to hydrolysis than the amino amides, are metabolized in the plasma by cholinesterases . The metabolites of the amino esters are derivatives of 4-aminobenzoic acid (PABA) and these substances are capable of inducing allergic reactions in a small percentage of patients. The amino amides undergo enzymatic degradation in the liver and allergic reactions are rare.

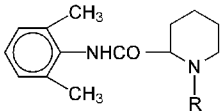
Table 3. Local Anesthetic Agents

Name	CAS Registry Number	Molecular formula	Structure number	Structure
procaine	[59-46-1]	C ₁₃ H ₂₀ N ₂ O ₂	(20, X = R, H, R' = C ₂ H ₅)	
chloroprocaine	[133-16-4]	C ₁₃ H ₁₉ ClN ₂ O ₂	(20, X = Cl, R = H, R' = C ₂ H ₅)	
tetracaine	[94-24-6]	C ₁₅ H ₂₄ N ₂ O ₂	(20, X = H, R = <i>n</i> -C ₄ H ₉ , R' = CH ₃)	

lidocaine	[137-58-6]	C ₁₄ H ₂₂ N ₂ O	(21, X = CH ₃ , R = H, R' = R = C ₂ H ₅)
prilocaine	[721-50-6]	C ₁₃ H ₂₀ N ₂ O	(21, X = H, R = C ⁺ H ₃ , R' = H, R = <i>n</i> -C ₃ N ₇)
etidocaine	[36637-18-0]	C ₁₇ H ₂₈ N ₂ O	(21, X = CH ₃ , R = R' = C ₂ H ₅ , R = <i>n</i> -C ₃ H ₇)



mepivacaine	[96-88-8]	C ₁₅ H ₂₂ N ₂ O	(22, R = CH ₃)
bupivacaine	[2180-92-9]	C ₁₈ H ₂₈ N ₂ O	(22, R = <i>n</i> -C ₄ H ₉)
ropivacaine	[84057-95-4]	C ₁₇ H ₂₇ N ₂ O	(22, R = <i>n</i> -C ₃ H ₇)



Pharmacological Profile. The profile of the ideal local anesthetic agent depends largely on the type and length of the surgical procedure for which it is applied (157). Procedures could include neuraxial (spinal and epidural) anesthesia, nerve and plexus blocks, or field blocks (local infiltration). In general, the ideal agent should have a short onset of anesthesia and be useful for multiple indications such as infiltration, nerve blocks, intravenous, extradural, spinal, and topical administration. The therapeutic indexes for systemic CNS and cardiovascular toxicity should be high and the agent should be compatible with the vasoconstrictor epinephrine.

The pharmacological profile of local anesthetic agents depends largely on the physicochemical properties given in Table 4 (153). Lipophilicity appears to be the primary determinant of *in vitro* (isolated nerve) potency. Agents which are lipophilic penetrate nerve membranes more easily than more hydrophilic compounds resulting in a greater concentration of agent at the interior sodium ion channel receptor. The *in vivo* potency, however, is also dependent on such other factors as vasodilator and tissue redistribution properties. The duration of anesthesia is primarily dependent on the agent's protein binding capability. Long duration agents, eg, bupivacaine (22, R = *n*-C₄H₉) and tetracaine (20, X = H, R = *n*-C₄H₉, R' = CH₃), appear to be more tightly bound to proteins than those possessing short durations such as procaine (20, X = R = H, R' = C₂H₅) and lidocaine (21, X = CH₃, R = H, R' = R = C₂H₅) hydrochloride.

Table 4. *In Vitro* Conduction Blocking and Physiochemical Properties of Local Anesthetic Agents^a

Agent	Conduction blocking properties ^b			Physiochemical properties		
	Potency	Onset	Duration	pK _a	Lipid solubility	Protein binding, %
procaine	1	1	1	8.9	0.6	5.8 ^c
mepivacaine	2	1	1.5	7.6	1.0	77 ^c
prilocaine	3	1	1.5	7.7	0.8	55 ^d
chloroprocaine	4	0.8	0.75	8.7		
lidocaine	4	0.8	1.5	7.7	2.9	64 ^d
tetracaine	16	2	8	8.5	80	76 ^d
bupivacaine	16	0.6	8	8.1	28	95 ^d
etidocaine	16	0.4	8	7.7	141	94 ^d

^a Ref. 153.
^b Relative to procaine. Data are derived from isolated frog sciatic nerve.
^c Nerve homogenate binding.
^d Plasma protein binding.

The rate of onset of local anesthetic activity *in vitro* is primarily determined by the pK_a of the local anesthetic agent. The protonated species of the agent is the active form whereas the free base possesses little or no activity. However, it is the basic form of the drug which diffuses through the nerve sheath. Consequently the higher the concentration of the free base, ie, the lower the pK_a, the more rapid is the onset of anesthesia. The *in vivo* onset is also determined by the nonnervous tissue diffusability of the compound. Many long duration local anesthetics exhibit long anesthetic onsets. Mixtures of these long duration agents and a short duration drug possessing a rapid onset have been used.

The rate of removal of the local anesthetic from the site of injection also affects its profile. All local anesthetic agents possess some vasodilatory activity at clinically useful concentrations. Agents which are more potent in this regard tend to be absorbed more rapidly by the vasculature. They are less potent anesthetics and have shorter durations than those having lower vasodilatory activity. A comparison of potency, onset, and duration as a function of physiochemical properties is presented in Table 4.

Another clinical consideration is the ability of local anesthetic agents to effect differential blockade of sensory and motor fibers. In surgical procedures such as obstetrics or postoperative pain relief, an agent which produces profound sensory block accompanied by minimal motor block is desirable. On the other hand some procedures such as limb surgery require both deep sensory and motor blockade. In clinical practice, bupivacaine (22, R = *n*-C₄H₉), in low doses, exhibits the former behavior and is used primarily as an extradural agent in obstetrics. The lowest effective extradural concentration of etidocaine (21, X = CH₃, R = R' = C₂H₅, R = *n*-C₃H₇), however, shows both adequate sensory and profound motor blockade so that it is useful in surgical situations where maximum neuromuscular blockade is necessary. In an isolated nerve preparation, bupivacaine blocks unmyelinated C fibers which are mainly responsible for pain perception at a much greater extent than the myelinated A fibers which carry motor impulses. It is postulated that absorption of bupivacaine by the vasculature at the site of injection, combined with the slow diffusion of this agent, results in an insufficient amount of the drug penetrating the large A fibers to cause motor conduction blockade. Clinically, motor block can be observed in some procedures.

Specific Local Anesthetic Agents. Clinically used local anesthetics and the methods of application are summarized in Table 5. Procaine hydrochloride [51-05-8] (Novocain), introduced in 1905, is a relatively weak anesthetic having a long onset and short duration of action. Its primary use is in infiltration anesthesia and differential spinal blocks. The low potency and low systemic toxicity result from rapid hydrolysis. The 4-aminobenzoic acid

formed is, however, thought to be responsible for allergic reactions caused by the drug.

Table 5. Clinically Used Local Anesthetic Agents

Agent	Method of application	Comment
<i>Amino esters</i>		
procaine	infiltration, spinal	slow onset, short duration
chloroprocaine	peripheral nerve and obstetric	fast onset, short duration, low systemic toxicity
tetracaine	extradural spinal	slow onset, long duration, high systemic toxicity
<i>Amino amides</i>		
lidocaine	infiltration, iv regional, peripheral nerve block, extradural block, spinal and topical	fast onset, moderate duration, low systemic toxicity, most versatile agent
mepivacaine	infiltration, peripheral nerve block, extradural	similar to lidocaine
prilocaine	similar to lidocaine	safest amino amide, methemoglobinemia at high doses
bupivacaine	infiltration, peripheral nerve block, extradural	moderate onset, long duration, potential for cardiovascular side effects, sensory motor separation
etidocaine	infiltration, peripheral nerve block, extradural	fast onset, long duration, profound motor block

Chloroprocaine hydrochloride [3858-89-7] is characterized by low potency, rapid onset, short duration of action, and low systemic toxicity. It is indicated for infiltration anesthesia at 1–2% and for extradural anesthesia at 2–3% when short surgical procedures are performed under regional anesthesia. Chloroprocaine may be mixed with long duration agents such as bupivacaine (22, R = *n*-C₄H₉) to afford a more rapid onset and shorter duration of action than bupivacaine alone.

Tetracaine (20, X = H, R = *n*-C₄H₉, R' = CH₃) is primarily used in spinal anesthesia providing a slow onset, high potency, and a long duration of action. Its potential for systemic toxicity limits its use in other forms of regional anesthesia. Tetracaine possesses excellent topical anesthetic activity and has been used in endotracheal surface and ophthalmic anesthesia.

Lidocaine hydrochloride [73-78-9] (Xylocaine), is the most versatile local anesthetic agent because of its moderate potency and duration of action, rapid onset, topical activity, and low toxicity. Its main indications are for infiltration, peripheral nerve blocks, extradural anesthesia, and in spinal anesthesia where a duration of 30 to 60 min is desirable. Because of its vasodilator activity, addition of the vasoconstrictor, epinephrine, increases the duration of action of lidocaine markedly. It is also available in ointment or aerosol preparations for a variety of topical applications.

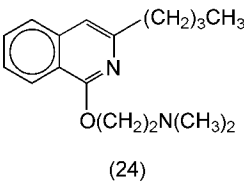
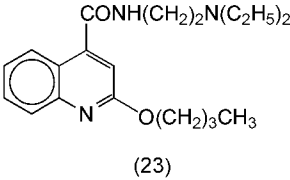
Mepivacaine hydrochloride [1722-62-9], similar in profile to lidocaine, is used for infiltration, peripheral nerve blocks, and extradural anesthesia. It appears to be less toxic than lidocaine in adults but more toxic in newborns. The duration of action is longer than that of lidocaine because of its lower vasodilator activity. Mepivacaine has little topical activity.

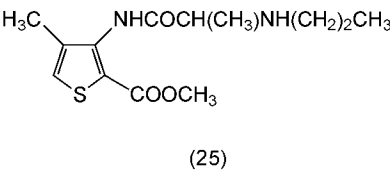
Prilocaine hydrochloride [1786-81-8] is also similar in profile to lidocaine, although prilocaine has significantly less vasodilator activity. Prilocaine is the least toxic of the amino amide local anesthetics. However, its tendency to cause methemoglobinemia, especially in newborns, has eliminated its use in obstetric surgery.

Bupivacaine hydrochloride [14252-80-3] (Marcaine), one of the most potent and longest duration agents in clinical use, is also one of the most toxic. The onset of anesthesia is moderate to long, but it is generally acceptable. Applications include infiltration, peripheral nerve blocks, extradural, and spinal anesthesia at 0.25 to 0.75%, although use at the high concentration is limited by the tendency to produce profound cardiovascular toxicity upon overdose. Advantages are in extradural obstetric procedures and postoperative pain relief because bupivacaine produces profound sensory but little motor block. Additionally, its high efficacy and long duration of action decreases the need for repeated injections.

Etidocaine (21, X = CH₃, R = R' = C₂H₅, R = *n*-C₃H₇), characterized by high efficacy, short onset, and long duration of action, may be used for infiltration, peripheral nerve block, and extradural anesthesia at 1.5 percent. Both sensory and profound motor block result. Thus this agent is useful only in procedures such as lower limb orthopedic and abdominal surgeries where neuromuscular blockade is necessary.

Anesthetic Agents Under Development. Ropivacaine (AL-381) (22, R = *n*-C₃H₇), similar in structure to mepivacaine and bupivacaine, has potency, duration, and CNS and cardiovascular toxicity somewhat lower than those of bupivacaine. Thus the advantage of ropivacaine is the significantly higher cardiovascular and CNS therapeutic indexes (158). Carbizocaine [76629-87-3] (BK-95), C₂₁H₃ N₂O₃, (23) is an amino carbamate possessing high potency as a topical, infiltration, and peripheral nerve blocking agent. Its potency in the rat sciatic nerve block test is ten times higher than that of bupivacaine (159). Heptacaine [55792-21-7], C₂₁H₃ N₂O₃, (24), also an amino carbamate, is somewhat more potent and has a slightly longer duration of action than lidocaine. The acute toxicity of heptacaine is comparable to that of lidocaine (160). Carticaine [23964-58-1/ C₁₃H₂₀N₂O₃S, (25) may be useful as an infiltration anesthetic with a somewhat longer duration of action than lidocaine and similar toxicity (161).





Economic Aspects

The total U.S. market value for the anesthetic agents listed was \$299.9 million in 1990 (162). General inhalation agents, valued at \$154.5 million, comprised over half (51.5%) of the 1990 market. General iv anesthetics were valued at \$111.5 million (37.2%). Local injectable agents, at \$33.9 million, represented the smallest portion of the market (11.3%). U.S. sales for selected anesthesia pharmaceuticals are given in Table 6.

Table 6. 1990 U.S. Sales for Anesthetic Drugs^a

Drug	Market value, \$ × 10 ⁶
<i>Inhalational agents</i>	
fluothane (halothane)	2.5
ethrane (enflurane)	18.1
forane (isoflurane)	133.9
<i>Injectable (iv) agents</i>	
pentothal (thiopental)	26.0
diprivan (propofol) ^b	29.0
sublimaze (fentanyl)	19.9
alfenta (alfentanyl)	8.6
sufenta (sufentanyl)	28.0
<i>Local injectable</i>	
novocain (procaine)	0.7
xylocaine (lidocaine)	22.5
marcaine (bupivacaine)	10.7

^a Ref. 162. Actual 1990 sales figures, generic and name brand products combined.

^b Launched November 1989.

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ANETHOLE.

See ETHERS.

ANILINE AND ITS DERIVATIVES.

See AMINES, AROMATIC AMINES, ANILINE AND ITS DERIVATIVES.

ANIMAL FEEDS.

See FEEDS AND FEED ADDITIVES.

ANOREXIANTS.

See ANTIOBESITY AGENTS.

ANSAMACROLIDES.

See ANTIBIOTICS, ANSAMACROLIDES.

ANTACIDS, GASTRIC.

See GASTROINTESTINAL AGENTS.

ANTHRACENE.

See HYDROCARBONS.

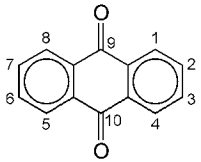
ANTHRAQUINONE

In the early part of the nineteenth century, as a result of the use of illuminating gas for lighting purposes, huge quantities of coal tar became available. Many different compounds were isolated from this tar, one of which was anthracene. In 1840, Laurent treated anthracene with nitric acid and obtained a compound which he named "anthracenuse" indicative of its source (*anthra*, Greek for coal). Another investigator called the new compound "oxyanthracen," and it was not until 1869 that Graebe and Liebermann, in the course of their investigation on quinones, named it anthraquinone. They obtained anthraquinone by oxidizing anthracene with bichromate and sulfuric acid which later became the first commercial method for the manufacture of anthraquinone from anthracene (1).

Anthraquinone [84-65-1] has yet to be found in nature, although some of its substitution products have been known since antiquity (alizarin, kermes, cochineal, and lac dye). Of all the quinones found naturally, those derived from anthraquinone far exceed all others. Many of these are found in molds (2).

For many years, anthraquinone provided the dyestuff industry with one of the greatest and most prolific building blocks for the manufacture of valuable dyestuffs noted for their outstanding fastness properties. During the years 1941–1961, production remained fairly constant and averaged 1,305 t per year for anthraquinone and 2,477 t for its precursor, *o*-benzoylbenzoic acid (3). Since 1969, production figures have not been made public. However, in recent times, production has fallen off considerably due to the high cost of manufacturing and the discovery of other classes of dyestuffs with good fastness properties.

Anthraquinone, C₁₄H₈O₂, has been variously named 9,10-dihydro-9,10-diketoanthracene, 9,10-dihydro-9,10-dioxoanthracene, and 9,10-antracenedione:



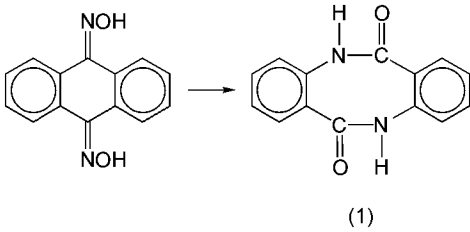
In the earlier literature, the 1,4,5,8 positions were known as alpha (α) and the 2,3,6,7 as beta (β). The 9,10-positions are known as meso- or ms-. Other quinones of anthracene are known, but only the 9,10-quinone is of technical importance.

Physical Properties

When sublimed, anthraquinone forms a pale yellow, crystalline material, needle-like in shape. Unlike anthracene, it exhibits no fluorescence. It melts at 286°C and boils at 379°–381°C. At much higher temperatures, decomposition occurs. Anthraquinone has only a slight solubility in alcohol or benzene and is best recrystallized from glacial acetic acid or high boiling solvents such as nitrobenzene or dichlorobenzene. It is very soluble in concentrated sulfuric acid. In methanol, uv absorptions of anthraquinone are at λ_{max} 250 nm (ϵ 4.98), 270 nm (4.5), and 325 nm (4.02) (4). In the ir spectrum, the double allylic ketone absorbs at 5.95 μm (1681 cm^{-1}), and the aromatic double bond absorbs at 6.25 μm (1600 cm^{-1}) and 6.30 μm (1587 cm^{-1}).

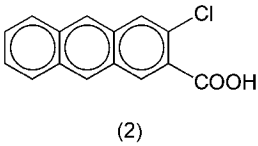
Chemical Properties

In general, anthraquinone is a relatively inert compound exhibiting stability towards oxidation. If this were not so, the commercial process for the production of anthraquinone by the oxidation of anthracene would never have achieved any technical importance. Many reactions of quinone compounds do not take place with anthraquinone or, if they do, it is only with difficulty. A monooxime is formed with hydroxylamine only by heating to a comparatively high temperature (5). A dioxime, 9,10-Autracedione dionene $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$, [7461-27-0] is formed by reaction of anthraquinone with hydroxylamine in polyphosphoric acid at 140°C (6). The dioxime undergoes the Beckmann rearrangement to give an 85% yield of dianthranilide [3266-71-5] (1) (7):

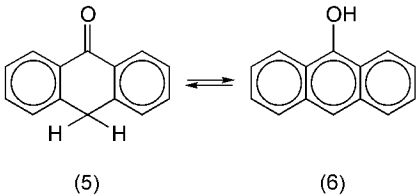
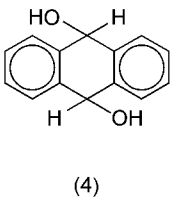
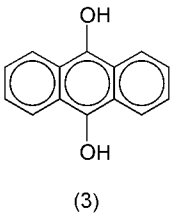


Indirect methods have also been used to form the monooxime (8) and the phenylhydrazone (9).

Only the reduction products involving the keto groups are of any academic or industrial importance. Complete reduction of the keto groups by ammonia and zinc (von Perger method) gives rise to anthracene in good yields and quality (10). This method is of importance since substituted anthracenes can be prepared from the corresponding anthraquinones. Industrially, an important dyestuff intermediate, 3-chloroanthracene-2-carboxylic acid, (2) is prepared by this method (11) from 3-chloroanthraquinone-2-carboxylic acid [84-32-2]



Depending on experimental conditions, sodium borohydride reduction of anthraquinone, in a lower aliphatic alcohol, results in 9,10-dihydroxyanthracene (3) [4981-662], 9,10-dihydro-9,10-dihydroxy-anthracene (4) [70143-55-4], anthrone (5) [90-44-8], and anthrol (6) [529-86-2] (12):

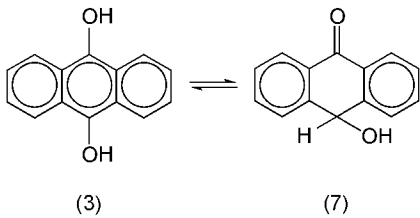


Other metal hydrides and metal alkoxides have been used as well as diphenylsilane and nickel–aluminum alloy (13).

Of special interest to the dyestuff chemist is the 9,10-dihydroxyanthracene structure since its red, water-soluble sodium salt forms the basis for applying anthraquinone dyes to cotton (qv). Because the reductions were originally carried out in large tubs or vats, the operation became known as "vatting" and the dyes as "vat" dyes. The most commonly used reducing agent is alkaline hydrosulfite, also known as dithionite ($\text{Na}_2\text{S}_2\text{O}_4$). Use of thiourea

dioxide, $\text{HN}=\text{C}(\text{SO}_2\text{OH})\text{NH}_2$, as a reducing agent has the advantage that the reduction can be carried out under acidic conditions (14). Because of its higher cost, its usage has been limited to a relatively few specialized cases.

Tautomeric with 9,10-dihydroxyanthracene, $\text{C}_{14}\text{H}_{10}\text{O}_2$, is oxanthrone [549-99-5] (7) which forms colorless needles, mp 167°C. The equilibrium mixture in alcoholic hydrochloric acid contains 97% 9,10-dihydroxyanthracene and 3% oxanthrone.



With concentrated sulfuric acid, anthraquinone forms oxonium salts, thus falling into a class of compounds known as " oxygen bases" (15). In an aqueous solution, anthraquinone has an ionization constant K_a equal to 7×10^{-23} and a pK_a of 7.4 (16).

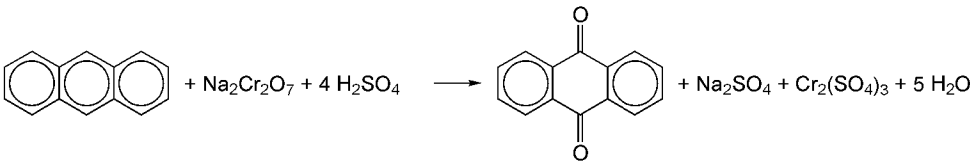
Anthraquinone can be sulfonated, nitrated, or halogenated. Sulfonation is of the greatest technical importance because the sulfonic acid group can be readily replaced by an amino or chloro group. Sulfonation with 20–25% oleum at a temperature of 130–135°C produces predominantly anthraquinone-2-sulfonic acid [84-48-0]. By the use of a stronger oleum, disulfonic acids are produced. The second sulfonic acid substituent never enters the same ring; a mixture of 2,6- and 2,7-disulfonic acids is formed (Wayne-Armstrong rule). In order to sulfonate in the 1-, 1,5-, or 1,8-positions, mercury or one of its salts must be used as a catalyst.

Anthraquinone disulfonic acids	CAS Registry Number
2,6	[14486-58-9]
2,7	[84-49-1]
1,5	[117-14-6]
1,8	[82-48-4]

Use of mercuric catalysts has created a serious pollution problem thereby limiting the manufacture of such acids. Other catalysts such as palladium or ruthenium have been proposed (17). Nitration of anthraquinone has been studied intensively in an effort to obtain 1-nitroanthraquinone [82-34-8] suitable for the manufacture of 1-aminoanthraquinone [82-45-1]. However, the nitration proceeds so rapidly that a mixture of mono- and dinitroanthraquinone is produced. It has not been possible, economically, to separate from this mixture 1-nitroanthraquinone in a yield and purity suitable for the manufacture of 1-aminoanthraquinone. Chlorination of anthraquinone cannot be used to manufacture 1-chloroanthraquinone [82-44-0] since polychlorinated products are formed readily. Consequently, 1-chloroanthraquinone is manufactured by reaction of anthraquinone-1-sulfonic acid [82-49-5] with sodium chlorate and hydrochloric acid (18).

Manufacture

Oxidation of Anthracene. Many oxidants have been described for the oxidation of anthracene [120-12-7] to anthraquinone, including nitric acid, molecular oxygen, ozone, chlorine, and dichromate (19). Industrially, only the use of dichromate achieved importance. Historically, this was the first process for converting anthracene to anthraquinone on an industrial scale (20): Water and sulfuric acid were added to an acid-proof kettle, equipped with a lead-covered steel agitator and a lead heating coil. To this was added 94–95% anthracene and a 20% solution of sodium dichromate. Under agitation and during six hours, the mixture was heated to 100°C. Frequent additions of dichromate were made until a permanent excess of dichromate was maintained for one-half hour. Then the reaction mass was filtered on an acid-proof filter box, washed free of acid, and dried. The chrome-containing filtrates were added to a large, lead-lined vessel where the chromium salts were precipitated by the addition of alkali, filtered, washed free of alkali, dried, and sold to the tanning industry as an economic credit against the cost of manufacturing the anthraquinone. Alternatively, the chromic acid may be regenerated electrochemically from the filtrates (21).



A 95% yield of pure anthraquinone was obtained. This is an almost quantitative yield based on the 100% content of the anthracene used. The crude anthraquinone was then purified. To a jacketed steel kettle, provided with an agitator, was added crude anthraquinone and nitrobenzene. Under agitation, the charge was heated at 130–140°C until a complete solution resulted. Under slow agitation, the solution was cooled to 30°C and the resulting slurry of anthraquinone was filtered on a pressure filter. The cake was washed twice with nitrobenzene, then was reslurried on the filter with nitrobenzene, sucked dry, and transferred to a vacuum dryer where the nitrobenzene was distilled. The dried anthraquinone was discharged to suitable containers. A 99% yield of pure anthraquinone was obtained equal to a recovery of approximately 90% based on the crude anthraquinone.

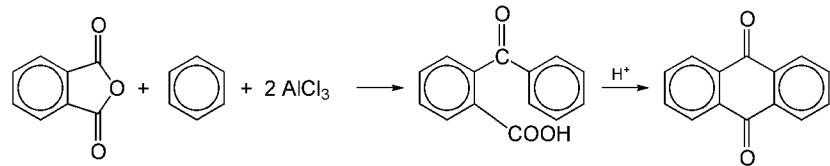
In Europe, where an abundant supply of anthracene has usually been available, the preferred method for the manufacture of anthraquinone has been, and still is, the catalytic oxidation of anthracene. The main problem has been that of obtaining anthracene, C₁₄H₁₀, practically free of such contaminants as carbazole and phenanthrene. Many processes have been developed for the purification of anthracene. Generally these follow the scheme of taking the crude anthracene oil, redistilling, and recrystallizing it from a variety of solvents, such as pyridine (22). The purest anthracene may be obtained by azeotropic distillation with ethylene glycol (23).

The catalytic oxidation of anthracene has received more attention than any other method for converting anthracene to anthraquinone. This is evident from the great number of patents issued on this method (24). Catalysts proposed for the oxidation generally utilize vanadium, either as its oxide or in the form of metal vanadates, in combination with the salts of other metals (iron, manganese, potassium, etc) supported on an inert carrier such as silica gel or aluminum hydroxide. The patent literature indicates that the ideal catalysts is one that does not require regeneration too frequently, that is not poisoned by impurities in anthracene, and that allows the oxidation of large volumes of anthracene per unit of time without the attendant production of appreciable quantities of phthalic anhydride. Unless the quality of the anthracene and the operating conditions are carefully controlled, the resulting anthraquinone may be contaminated. Such contaminants have been isolated and identified (25). Crude anthraquinone may be purified by various methods, such as sublimation (26).

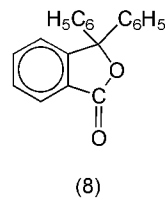
The vapor-phase catalytic oxidation of anthracene to anthraquinone was first described in 1916 and was the basis for a plant operated at Ludwigshafen (27). In 1940, a smaller plant at Milan, Italy incorporated the latest information available at the time and was believed to be far in advance, technically, of the Ludwigshafen plant. The entire plant was designed exclusively for the manufacture of anthraquinone from anthracene (28). The main feature of the plant was the so-called "contact oven" where the oxidation of the anthracene occurred. The oven was a cylindrical iron vessel about 5.8 m high and 2.4 m in diameter. Within the oven were nine perforated sheet-iron shelves placed one on top of the other. On each shelf was a layer of iron vanadate catalyst (29) embedded in high pressure coils which heated and cooled the reaction mass during the oxidation. In conjunction with the contact oven were a number of auxiliary pieces of equipment: a preheater for heating an air–steam mixture, a vaporizer containing molten anthracene, various metering and temperature control devices, several heat exchangers, and a Dowtherm heating system. Briefly, 93% anthracene was vaporized at 318°C by means of the preheated air–steam mixture. The steam was incorporated to minimize the possibility of an explosion during the oxidation; several had

occurred at the Ludwigshafen plant. The vaporized anthracene–air–steam mixture was carefully metered into the contact oven containing the catalyst at 390°C. From here, the anthraquinone–air–steam reaction mixture passed through several heat exchangers and finally into a cold room where the anthraquinone was deposited. The yield of anthraquinone was about 82° of theory and had a purity of 99.6°. Although the yield was lower than that obtained by the dichromate oxidation, the vapor-phase catalytic oxidation had the advantage that no by-products were formed. A pilot plant has been described for the fluid-bed, vapor-phase catalytic oxidation of anthracene. The process gave a 96° yield of anthraquinone having a purity greater than 90° (30). Anthracene has been oxidized to anthraquinone electrolytically using ceric sulfate as a catalyst. Quantitative yields have been claimed (31). Laboratory procedures have been described for oxidizing anthracene to anthraquinone (32).

Friedel-Crafts Reaction. Until quite recently, the manufacture of anthraquinone in the United States was by the Friedel-Crafts reaction: benzene [71-43-2] and phthalic anhydride [85-44-9] condense in the presence of anhydrous aluminum chloride to give *o*-benzoylbenzoic acid [85-52-9] which, on treatment with concentrated sulfuric acid, is converted into anthraquinone in high yields and purity (33).



Unless two moles of anhydrous aluminum chloride are used per mole of phthalic anhydride, the yields of *o*-benzoylbenzoic acid are low due to the formation of diphenylphthalide (8) 596-29-2/ (34):



Both a ball mill and a solvent process have been described for the manufacture of *o*-benzoylbenzoic acid. In the latter method (35), an excess of dry benzene is charged into a jacketed, cast-iron reactor at room temperature. Granulated anhydrous aluminum chloride is added under agitation, followed by the addition of phthalic anhydride. Heat is evolved and is controlled until a temperature of 50–60°C is reached. The hydrogen chloride evolved is passed through a condenser in order to remove entrained benzene and finally into an alkaline scrubber which removes the hydrogen chloride. Heating is continued at 50–60°C until the evolution of hydrogen chloride has practically ceased. At this point, the charge is transferred to an acid-proof kettle containing dilute sulfuric acid. Here, the aluminum chloride complex of *o*-benzoylbenzoic acid decomposes giving a benzene solution of *o*-benzoylbenzoic acid and an aqueous solution of aluminum salts. After separation, the solution of aluminum salts may be used as a coagulant in the water-treatment plant. The benzene solution is transferred to another acid-proof vessel where the benzene is steam-stripped off, resulting in a slurry of *o*-benzoylbenzoic acid. This is filtered, washed acid-free, and dried. A very pure product is obtained in practically a quantitative yield. A typical unit for the manufacture of *o*-benzoylbenzoic acid is shown in Figure 1.

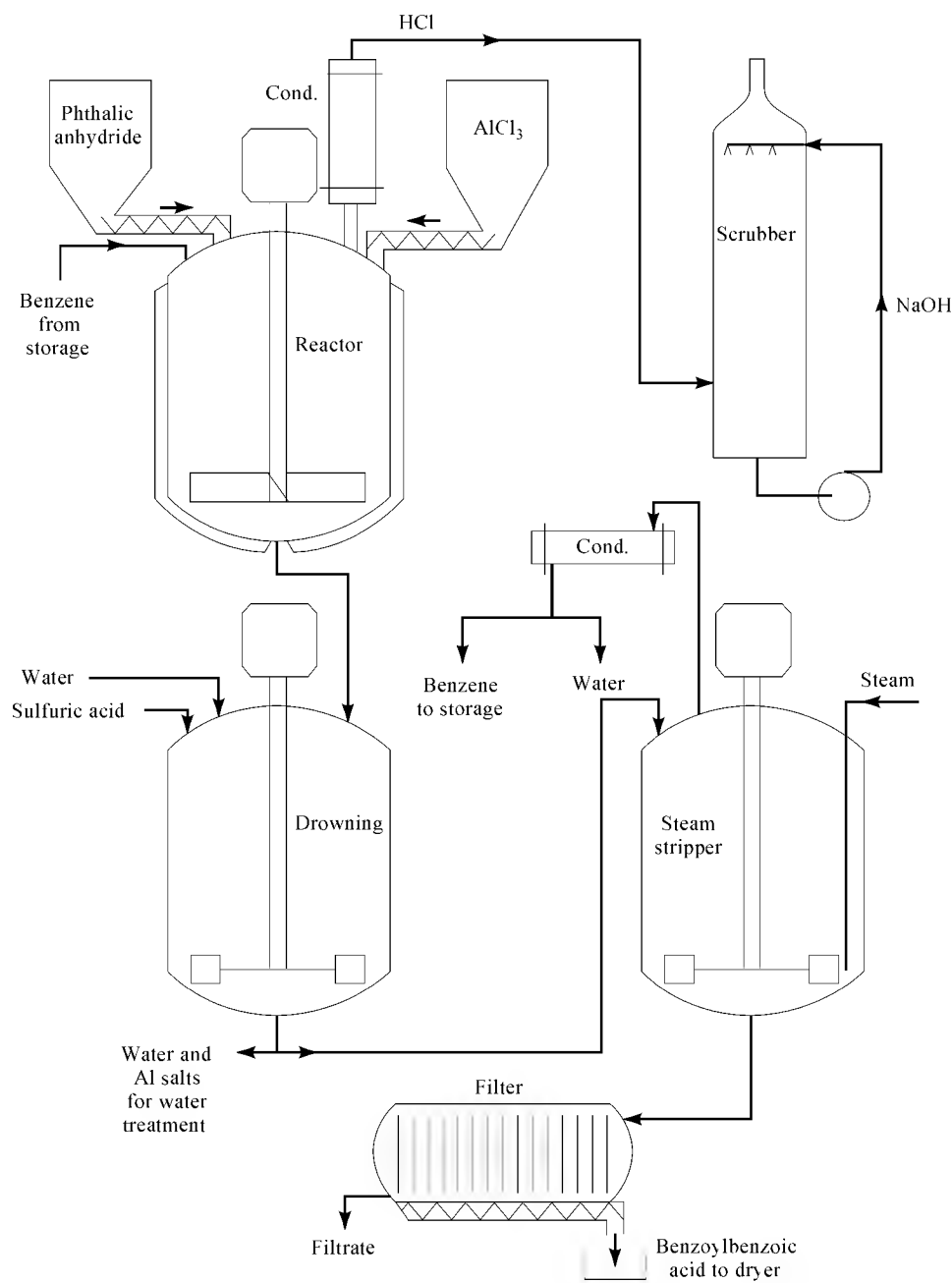


Fig. 1. *o*-Benzoylbenzoic acid manufacture.

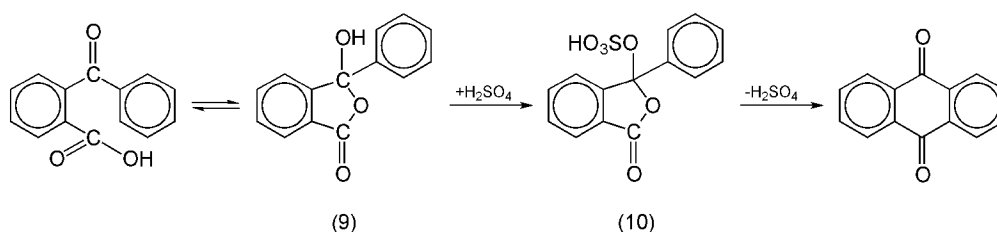
In the ball mill process (36), an iron, horizontal rotary-type reactor is used for the condensation. The mill is equipped with a calibrated vessel for feeding in benzene, an outlet pipe through which hydrogen chloride escapes from the mill into an alkaline scrubber, and a manhole for adding solid material. Inside the mill are iron balls or rods which stir the reactants during the condensation. Benzene, phthalic anhydride, and anhydrous aluminum chloride are charged into the mill in the molecular ratio of 1:1:2. These are slowly heated to 50–60°C and held there until no more hydrogen chloride is evolved. During the condensation, the hydrogen chloride mixes in the viscous mass causing it to form a spongelike material which fills the entire mill. As stirring continues, the aluminum chloride complex of *o*-benzoylbenzoic acid is ground into a powdery material which is discharged through a coarse sieve into suitable containers. Decomposition of the aluminum complex follows the same procedure as that described in the solvent process. The yield and quality of the product are equal to that obtained by the solvent process.

There are advantages and disadvantages in both processes: the solvent process requires no special equipment but uses an excess of benzene whose recovery adds to the cost of the product. The ball mill method uses no excess benzene but requires special equipment which has frequent mechanical problems.

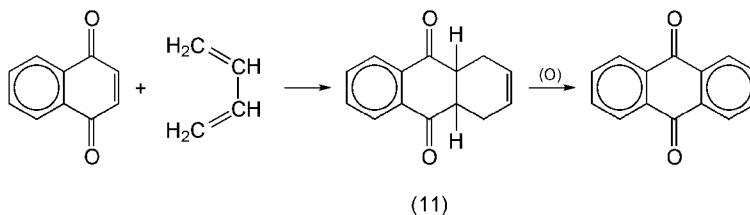
Benzene and phthalic anhydride may be condensed to *o*-benzoylbenzoic acid using hydrofluoric acid and boron trifluoride instead of anhydrous aluminum chloride (37).

Ring closure of *o*-benzoylbenzoic acid is accomplished by the use of concentrated sulfuric acid or a weak oleum (5–20%) solution at a temperature ranging from 100–110°C. Practically, a quantitative yield of very pure material is obtained (38). Also, the conversion can be accomplished by heating *o*-benzoylbenzoic acid at 200–300°C in the presence of a Lewis-type catalyst. High yields of anthraquinone are claimed (39). A one-step process has been described in which benzene is acylated by phthalic anhydride followed by ring closure of the resulting *o*-benzoylbenzoic acid. Briefly, in an atmosphere of nitrogen and carbon dioxide and at a temperature of 430°C, benzene and phthalic anhydride are passed over a catalyst consisting of magnesia, silica, metal oxides, and metal sulfates. A 90% conversion of the phthalic anhydride results giving an 88% yield of anthraquinone (40).

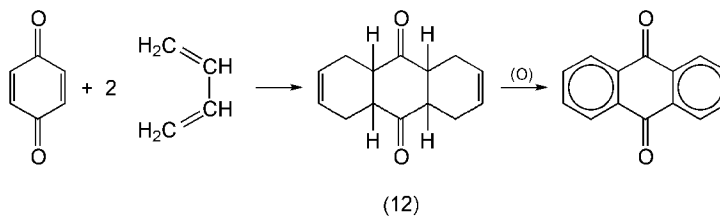
Ring closure of *o*-benzoylbenzoic acid to anthraquinone is an unusual reaction in that normally it is not predicted to occur ortho to a keto group. Several theories have been proposed to explain the mechanism whereby this could possibly occur. One involves a complex ionization of *o*-benzoylbenzoic acid (41), the other favors the intermediate formation of 3-hydroxy-3-phenyl-1(3*H*)isobenzofuranone (9) [64693-03-4] and 3-phenylphthalidyl sulfate (10) (42):



Diels-Alder Reaction. In 1928, Diels and Alder discovered that 1,3-unsaturated organic compounds reacted with quinoid systems to give partially hydrogenated, cyclic compounds. In the course of their work, they found that 1 mol of 1,4-naphthoquinone [130-15-4] reacted readily with 1 mol of 1,3-butadiene [106-99-0] to give a partially hydrogenated anthraquinone (11) 1,4,4a,9a-tetrahydro-9,10-anthracenedione [56136-14-2] which, on oxidation with chromic oxide, produced anthraquinone (43):



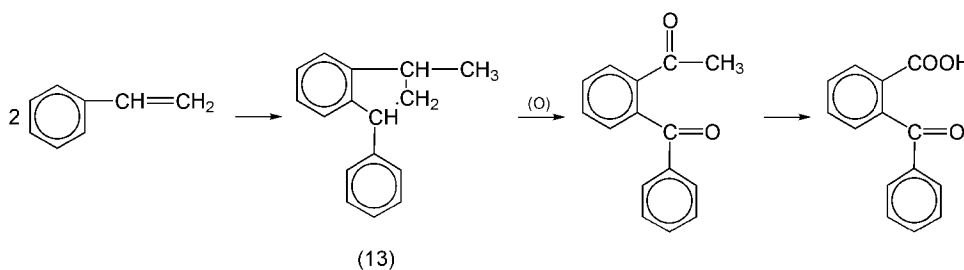
Although a patent was issued for the manufacture of anthraquinone by this method (44), it was never put into practice because, at that time, butadiene and naphthoquinone were not available at a reasonable price. However, during World War II there was a great demand for 1,3-butadiene in the manufacture of synthetic rubber. This resulted in the development of processes whereby it became a readily available intermediate at a fairly low cost. 1,4-Naphthoquinone is formed to some extent during the vapor-phase oxidation of naphthalene to phthalic anhydride. By varying the nature of the catalyst and other variables, it is possible to produce increasingly larger amounts of 1,4-naphthoquinone (45). American Cyanamid found that an impure 1,4-naphthoquinone, as obtained directly from the phthalic anhydride converter, could be condensed with 1,3-butadiene to give anthraquinone in almost theoretical yields and excellent purity (46). Based on this, American Cyanamid erected a plant for the manufacture of anthraquinone by the Diels-Alder reaction. Unforeseen technological problems developed which terminated the manufacture of anthraquinone by this method. European manufacturers also investigated the manufacture of anthraquinone by the Diels-Alder reaction. CIBA utilized a variation of the American Cyanamid patent (47) while BASF used *p*-benzoquinone [706-51-4] instead of 1,4-naphthoquinone (48). In this method, *p*-benzoquinone condenses with 2 mol 1,3-butadiene to give octahydroanthraquinone (12) [33982-93-3] which is then oxidized by oxygen, under pressure and in the presence of alkali, to give anthraquinone:



A continuous process has been described for the manufacture of anthraquinone by the Diels-Alder reaction (49).

The mechanism of the Diels-Alder reaction is not as simple as usually depicted. This may, in part, explain some of the problems encountered when this reaction has been applied on an industrial scale. A number of different theories have been proposed for this reaction (50).

Manufacture of *o*-Benzoylbenzoic Acid from 1-Methyl-3-phenylindane. In 1909 it was reported that treatment of styrene with concentrated sulfuric acid resulted in its dimerization (51). However, the wrong structure was assigned to this dimer (52). Years later it was suggested, without proof, that the dimer consisted primarily of 1-methyl-3-phenylindane (13) [6416-39-3] and some 1,3-diphenyl-1-butene (53). In 1950, oxidative studies on the dimer proved that this supposition was correct (54):



Under the oxidative conditions used, only low yields of *o*-benzoylbenzoic acid were obtained since this underwent further oxidation.

In the early 1970s, styrene was a fairly inexpensive intermediate (55); also 1-methyl-3-phenylindane could be obtained from styrene [100-42-5] in high yields (56). These facts, and the fact that supplies of anthracene were dwindling, led BASF to invest over three million dollars in research in an effort to develop a practical process for the oxidation of 1-methyl-3-phenylindane to *o*-benzoylbenzoic acid (57). Various oxidative techniques were developed: oxygen under pressure along with a catalyst (58), nitrogen dioxide and selenium (59), a solution of nitric and hydrochloric acids (60), and a combination of nitric acid and a dichromate (61). The latter method gave the highest yield of *o*-benzoylbenzoic acid—about 92% of theory. By 1972, BASF had a pilot in operation for the oxidation of 1-methyl-3-phenylindane to anthraquinone; however, unforeseen dermatological problems prevented the continuation of the operation (57).

Economic Aspects

In the dyestuff industry, anthraquinone still ranks high as an intermediate for the production of dyes and pigments having properties unattainable by any other class of dyes or pigments. Its cost is relatively high and will remain so because of the equipment and operations involved in its manufacture. As of May 1991, anthraquinone sold for \$4.4 kg in ton quantities. In the United States and abroad, anthraquinone is manufactured by a few large chemical companies (62). At present, only two processes for its production come into consideration: manufacture by the Friedel-Crafts reaction utilizing benzene, phthalic anhydride, and anhydrous aluminum chloride, and by the vapor-phase catalytic oxidation of anthracene; the latter method is preferred.

Health, Safety, and Environmental Factors

Anthraquinone is a comparatively safe compound: LD₅₀ (rat) is 3500 mg kg. It is a mild allergen and, as a fine powder, may cause skin irritation. It presents only a slight fire hazard on exposure to heat.

Of the two processes used for the manufacture of anthraquinone, the one involving the vapor-phase catalytic oxidation of anthracene has the least effect on health and the environment. On the other hand, the use of benzene in the Friedel-Crafts process presents serious safety and health problems: benzene is a highly flammable liquid having a flash point of -11°C. It has an upper explosive limit of 7.1% and a lower one of 1.3%. By OSHA standards, the average 8-h exposure limit is 10 ppm. Exposure to 3,000 ppm may be tolerated for only 30–60 min after which irritation of the nose, throat, and lungs may occur along with headaches, dizziness, and slurred speech. Exposure for 5–10 min at a concentration of 20,000 ppm results in death. Benzene is a known leukemogen (63). The workplace should be well ventilated and equipped with respirators capable of handling different concentrations of benzene.

Disposal of the solutions of aluminum salts generated in the Friedel-Crafts process presents an environmental problem unless use can be found for them as coagulants in a water treatment plant.

Uses

Aside from its major use in the manufacture of intermediates for anthraquinone dyes and pigments, anthraquinone is finding increasing interest as a catalyst in the pulping of wood (64), in the polymerization of various materials for plastics (65), and in the isomerization of vegetable oils (66). It has been used to make seeds distasteful to birds (67) and as an accelerator in nickel electroplating (68).

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A. J. Cofrancesco

ANTHRAQUINONE AND RELATED QUINOID DYES.

See DYES, ANTHRAQUINONE.

ANTHRAQUINONE DERIVATIVES.

See DYES, ANTHRAQUINONE.

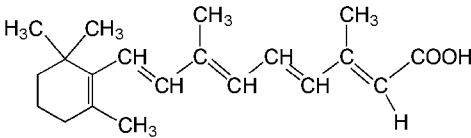
ANTIAGING AGENT

The human aging process is extremely complex and appears to affect all bodily functions equally; there are no known tissues that appear to age significantly faster than others. Statistically, the aging process is described most often by the exponential increase in death rate with advancing age. This results in the risk of death from all causes doubling every eight or nine years in humans. More important, however, are the declines associated with the aging process, which have focused historically on such clearly demonstrable end points as the progressive decline in vigor, health, and sensory, cognitive, and motor functions. However, the tremendous advances in molecular biology over the past decade have made it possible to begin to study the basic mechanisms of aging at the molecular level and relate those findings to specific age-related diseases at the cellular, tissue, and organ level. It is likely that these advances will demonstrate that there are multiple mechanisms underlying the aging process at all levels and that multiple interventions will therefore be necessary to arrest, slow, or reverse the aging process. Factors already known to be intimately involved in the aging process include environmental, dietary, and genetic influences; each appears to be involved in the various age-related disease states to a greater or lesser degree. Consequently, no single agent is likely to be found that will arrest or reverse all aging processes. Indeed, current research efforts in the discovery of antiaging agents focus mostly on modulation of single aging processes and the effects of such modulation on one or two major organ systems of the body. Agents are discussed here relative to the prevention and treatment of the aging process and age-related disorders characteristic of the principal organ systems that are most affected.

Skin

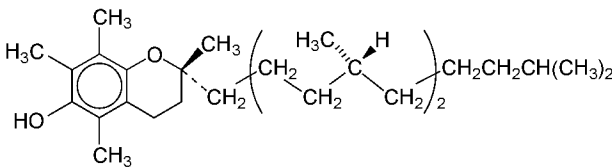
The characteristics of chronologically aged skin should be differentiated from the features of photoaging, which is marked by yellowed, leathery, sagging, wrinkled, elastotic skin, as well as underlying dermal connective tissue matrix damage and various benign, premalignant, and malignant neoplasms (1). There is a great increase in glycosylaminoglycans in photodamaged skin, whereas there is little change in aged, sun-protected skin. Thus it is essential to distinguish intrinsic aging from age-dependent abnormalities; in this case, the cumulative assault of sunlight on the skin. A brief review of these differences has appeared (2).

Tretinoin, the all-*trans* isomer of retinoic acid [302-79-4], was shown in the 1960s to be useful for the treatment of disorders associated with abnormal epithelial differentiation.

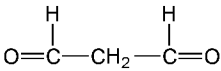


However, because of irritation, retinoids were only slowly accepted. In the 1970s, evidence accumulated to show that topical tretinoin could modulate many of the abnormalities in the epidermis and dermis associated with photoaging. It has been shown in hairless mice that tretinoin can reverse dermal elastosis with the formation of the new collagen and this had led to clinical trials being carried out in humans (3). Randomized controlled trials in human subjects have shown that topical tretinoin (0.1% cream) treatment in reversing some histologically and clinically apparent changes in photoaging such as fine and coarse wrinkling, skin color, and surface texture (4). These changes are thought to be the result of an augmentation of the natural repair process in the photoaged skin. In addition, studies in animals and humans indicate that tretinoin appears to retard melanoma growth and metastasis and to normalize the histologic appearance of dysplastic nevus cells (5). Aging is associated with impairment of immune functions, the most significant changes being a decrease in T-cell mediated immunity. Elderly subjects are increasingly susceptible to cutaneous pathological changes that are known to correlate with immune deficiencies, such as viral and fungal infections, and skin cancers. The pathophysiology of these deficiencies in the skin's immune system in the elderly is not clear; it may reflect not only a general decline in the immune system but also more specific changes such as the observed age-related changes in the morphology and function of the Langerhans cells and the decreased production of cytokines (6).

Vitamin E [59-02-9], C₂₉H₅₀O₂, has been studied for its potential to modulate prostaglandin metabolism and alter immune response in aged mice.



Results show that vitamin E enhances various immune functions (both T- and B-cell dependent) in aged mice and the enhancement appears to be mediated by decreased prostaglandin synthesis (7). Vitamin E has long been studied as an antioxidant and free-radical scavenger in the suppression of cell membrane unsaturated lipid peroxidation and it is likely that the inhibition of prostaglandin synthesis by vitamin E is due to these properties. One of the deleterious consequences of lipid peroxidation is thought to be the formation of malondialdehyde [542-78-9] which then forms Schiff bases with primary amino groups of proteins and other macromolecules resulting in cross-linking.



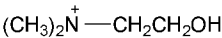
The age pigments (lipofuscin), which accumulate with age, are largely made up of these precipitated lipid-protein complexes resulting from such cross-linking. Vitamin E may function to help prevent formation of these complexes. The metabolic role of antioxidants (qv) such as vitamin E in animal tissues, however, remains quite controversial.

Sunscreens block the cutaneous absorption of ultraviolet (uv) light radiation (280–315 nm) and prevent sunburning, premature aging, and cancer of the skin (see COSMETICS). Photoaged skin, long believed to be irreversibly damaged, has now been shown to undergo significant repair when uv exposure are stopped. In the hairless mouse model, sunscreens prevented photoaging and allowed natural repair to occur (8). A study in young and old rats to compare the capacity of skin fibroblasts and epidermal keratinocytes to remove low levels of uv-induced DNA damage (pyrimidine dimers) from their DNA, *in vitro* and *in vivo*, showed that the repair mechanism in the old appeared to be as efficient as that in the young animals. However, a considerable fraction of dimers persists in both cell types and therefore there is the possibility that long-term exposure of skin cells to uv may lead to an accumulation of DNA damage with age (9).

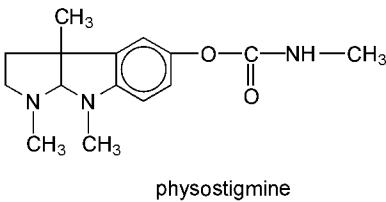
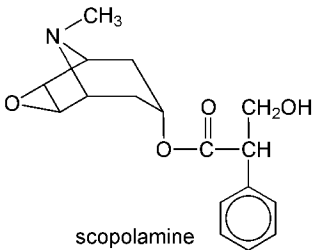
Central Nervous System

Aging is associated with progressive deterioration in CNS function. A number of factors besides genetic considerations contribute to those degenerative changes including nutritional elements and environmental toxins. The blood-brain barrier (BBB) is a major modulator of nutrient delivery to the CNS. Senescence is associated with significant changes in BBB function including a decrease in BBB choline transport and brain glucose influx (10). There appears to be an age-related decrease in the rate of metabolic protein synthesis in the brain as studies have demonstrated a two- to threefold decrease in the rate of synthesis in all brain areas in old as compared to young rats (11). Senile or neuritic plaques are a pathological feature of the aging brain and consist of abnormal neuritic and glial processes surrounding an extracellular core of material with fibrillary ultrastructure. Present at low densities in the cerebral cortex of most aged individuals, these plaques occur in large numbers in Alzheimer's disease , the major form of senile dementia. This disease is marked by deterioration of brain tissue and the characteristic loss of memory is due to neurotransmitter failure. Interestingly, the presence of aluminosilicates has been confirmed in brain tissues from patients with Alzheimer's disease and has been suggested as an early and essential factor in the pathogenesis of Alzheimer-type changes in the CNS (12).

Cholinergic mechanisms have long been studied with respect to memory and learning. An interesting study demonstrated that the age-related decline in memory observed in laboratory rodents can be reversed by administration of choline [62-49-7] (13).



Another study in rats showed that working memory and performance in a T-maze were significantly impaired with age, that physostigmine, a cholinesterase inhibitor, enhanced working memory in middle-aged and old rats, whereas scopolamine [51-34-3], an anticholinergic agent, impaired memory in young, middle-aged, and old rats. Physostigmine [57-47-6] reversed the scopolamine impairments of working memory (14).



These studies confirm that enhancing the cholinergic system could lead to reversal of age-related memory loss. Direct and indirect evidence indicating an activation of cholinergic mechanisms exist for pyrrolidinone derivatives including piracetam, oxiracetam, aniracetam, pyroglutamic acid, tenilsetam, and pramiracetam, and for miscellaneous chemical structures such as vinpocetine, naloxone, ebitaride (a hexapeptide), and phosphatidylserine (Table 1).

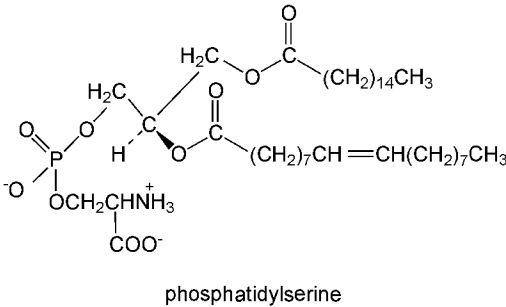
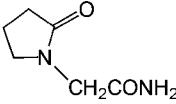
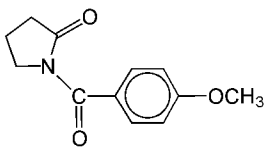
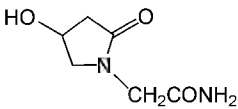
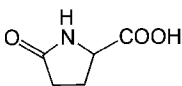
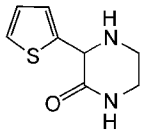
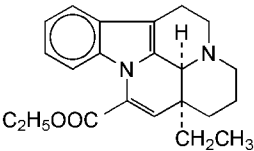
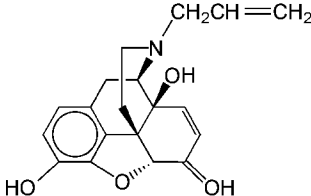
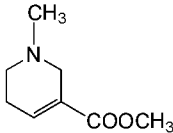
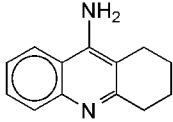
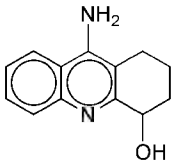


Table 1. Activators of Cholinergic Mechanisms

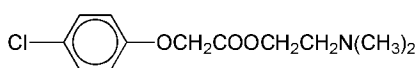
Name	Molecular formula	CAS Registry Number	Structure
piracetam	C ₁₀ H ₁₀ N ₂ O ₂	[7491-74-9]	

aniracetam	$C_{12}H_{13}NO_3$	[72432-10-1]	
oxiracetam	$C_6H_{10}N_2O_3$	[62613-82-5]	
L-pyroglutamic acid	$C_5H_7NO_3$	[98-79-3]	
tenilsetam	$C_8H_{10}N_2OS$	[86696-86-8]	
vinpocetine	$C_{22}H_{27}N_2O_2$	[42971-09-5]	
naloxone	$C_{19}H_{21}NO_4$	[465-65-6]	
arecoline	$C_8H_{13}NO_2$	[63-75-2]	
tacrine	$C_{13}H_{14}N_2$	[321-64-2]	

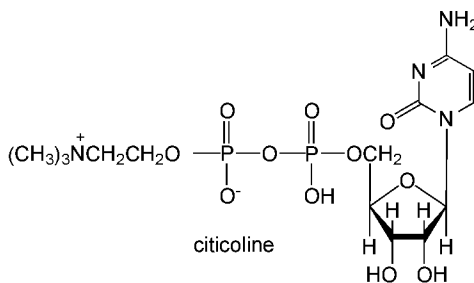
All these drugs prevent scopolamine-induced disruptions of several learning and memory paradigms in animals and humans (15). Piracetam, one of the most studied nootropic agents, has been reported to elevate muscarinic cholinergic receptor density in brain tissue of old but not young mice (16); this could partly explain the positive effects of the drug on memory and other cognitive functions. Hydergine, a mixture of ergot alkaloid mesylates, has also been shown to restore muscarinic cholinergic receptors in the hippocampus of old rats (17) and a five-year clinical study in about 89 elderly subjects showed that performance in some psychometric tests was better in the treated group than in the placebo group (18). Tetrahydroaminoacridine (tacrine) has been studied in Alzheimer's disease where it shows some degree of efficacy (19) and is thought to be a cholinesterase inhibitor. A recent study in rats, however, indicates that tacrine improves cognitive function without significant change in brain acetylcholine content (20). A drug combination study in old mice using tacrine and arecoline showed that the combination could enhance memory processing better than either drug alone (21). Another promising candidate in this class of acetylcholine esterase inhibitors is velnacrine ($C_{13}H_{14}N_2O$) (9-amino-1,2,3,4-tetrahydroacridin-1-ol) which is presently in human clinical testing in the United States for Alzheimer's disease.



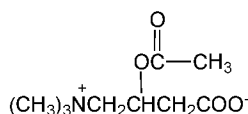
The combination of meclofenoxate [51-68-3] and citicoline [987-78-0] has been reported to enhance learning and memory retention in aged rats (22).



meclofenoxate



The ergot alkaloid dihydroergocryptine, a form of hydergine, has shown potent dopaminergic activity and improves motor performance and coordination of aged rats (23). Perhaps one of the most promising drugs for improving the mental impairments of aging in animals and humans is acetyl-L-carnitine [14992-62-2] (ALCAR).



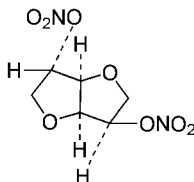
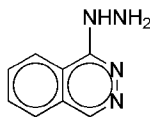
Rats treated for eight months with ALCAR had less age-related deterioration in their ability to learn and solve a radial maze (24) and showed a preservation of their spatial learning abilities (25). After oral treatment for six months, 20 patients with decreased motor activities showed ALCAR to be significantly effective in improving cognitive ability, depression, and behavioral and self-sufficiency performances, achieving recovery of the patients' quality of life (26). A three-month double-blind study in 30 patients suffering from mental impairment showed that the ALCAR treated group achieved a significant improvement over placebo in behavioral performances, memory tests, attention tests, and in the verbal fluency test (27). Interestingly, ALCAR administration in rats for 11 months significantly reduced the accumulation of lipofuscin within the brains of treated versus control animals (28).

Free radicals have been implicated in the pathogenesis of a number of neuropsychiatric disorders including aging of the CNS (29). The known nootropic effects of the drug centrophenoxine (an alternative name for medofenoxate), a form of dimethylaminoethanol ($(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{OH}$), can be interpreted on the basis of its OH radical scavenger properties and is thus thought to act as a protective agent of neuronal membranes into which it is incorporated in the form of phosphatidyl dimethylaminoethanol (30). At the molecular level, prevention of cross-linking of proteins is viewed as a major beneficial antiaging effect of centrophenoxine.

Cardiovascular System

Cardiovascular disease remains the most common age-related disease of all major disease types and is the most common cause of morbidity and mortality in old age. Besides age, however, risk factors that initiate and aggravate cardiovascular disease include hypertension, personality traits, genetics, diet, smoking, obesity, physical indolence, dyslipidemia, impaired glucose tolerance, and sex. Most risk factors are more prevalent in the elderly than in the young adult. Only one independent factor, hypercholesterolemia, has been linked definitively to increased mortality due to myocardial infarction (31). The management of elevated blood lipids therefore represents a most important objective in the prevention and treatment of cardiovascular disease. A concise review of pharmacological agents such as lovastatin [75330-75-5] for the treatment of hypercholesterolemia has appeared (32) (see **CARDIOVASCULAR AGENTS**). In addition, antiatherosclerogenic diets low in saturated fat and cholesterol, rich in fiber, and with substitution of polyunsaturated fat and restricted calories tend to normalize serum lipids and to cause lesions to involute (33).

A review of cardiac failure and the mechanism of the dysfunction of the heart and the vasculature has pointed out that a knowledge of cellular and subcellular mechanisms is critical if alteration and corrective therapies can effect modulation of the aging process (34). Cardiac failure is not a simple process. The involvement of other organ systems such as the autonomic nervous system, endocrine, kidney, and regional vasculature is very important. However, whatever the etiology, one important feature of aging is the remodeling of the ventricle and blood vasculature. Various agents such as vasodilators, hydralazine [86-54-4] and isosorbide dinitrate [87-33-2] (35) have been used.



Other possibilities include α blockers (36) and calcium antagonists (37). Other unproven agents include the β -adrenoreceptor agonists, phosphodiesterase inhibitors that affect movement of sodium and potassium through cellular channels, and calcium contractile protein sensitizers (38). Any of these agents and the appropriate cellular mechanisms that prevent or slow morphologic alteration in the heart or blood vessels should counteract the aging process.

Immune System Normal aging is associated with a gradual decline in the immune response of all species studied including humans. This decline appears to affect all levels of the system as expressed on the molecular level by decreased messenger RNA and protein synthesis and degradation, on the biochemical level by impaired metabolic pathways, on the cellular level by impaired mitogenesis, and on the organismic level by association with numerous immune-related diseases including infections, cancer, and autoimmune disorders (39). The general immune system decline begins in humans at puberty, which coincides with the maximum development of the thymus. In general, there is a decrease in the magnitude of the immune response that tends to affect T-cell-dependent functions to a greater extent than T-cell-independent functions. Thus delayed hypersensitivity and T-cell-mediated cytotoxicity are depressed to a greater extent than is antibody production (40). Because of the important role that the immune system plays with respect to overall health in the aged, a number of approaches have been devised to prevent the loss of immune responsiveness or to restore it once it is declining or has been lost. These immunological interventions have been reviewed (41).

One component of the age-related decline in immune function is decreased production of the lymphokine that promotes the growth of T-cells, interleukin 2 (IL-2). Administration of recombinant-derived IL-2, both *in vitro* and *in vivo*, appears to restore certain immune functions in aged mice. Recovery of T-regulatory effects on B-cell differentiation has been reported in human cells from elderly patients treated with IL-1 and or IL-2 (42). Similar effects have been observed in the presence of the pentapeptide thymopentin [69558-55-0] (Arg·Lys·Asp·Val·Tyr), a well-known IL-2 inducer. Recombinant IL-2 administered to aged mice for three weeks has been shown to correct the T-cell functional deficiency associated with antigen-specific immunoglobulin production by certain lymphoid tissue (43).

Reconstitution of T-cell deficiencies with thymic hormones has not been successful even though the various hormone preparations induce prothymocyte differentiation and functions of mature T-cells. They do not regulate the maturation of thymocytes in the thymus. In contrast, IL-2, endotoxin, thymic epithelial cell products, but not interleukin 1, were found to promote functional maturation of immature thymocytes. Two classes of drugs show thymomimetic actions (Table 2). Levamisole [14769-73-4], C₁₁H₁₂N₂S, and the sodium salt of diethyl dithiocarbamate (imuthiol) and certain other sulfur-containing compounds restore T-cell function via induction of a thymic hormonelike factor (44). Imuthiol [148-18-5], can also generate cytotoxic T-cells in athymic nude mice and in euthymic old animals (45). The other class consists of hypoxanthine derivatives such as isoprinosine and NPT 15392. These compounds induce T-cell maturation directly and promote T-cell function *in vitro* and *in vivo*. In subjects over 65 years of age with chronic diseases, isoprinosine significantly enhanced *in vitro* mitogen-induced proliferation of mononuclear cells (in this case mainly T-cells) (46). Bestatin [58970-76-6], a leucine derivative, has been shown to restore immune responsiveness in old mice and to prevent spontaneous tumor occurrence (47).

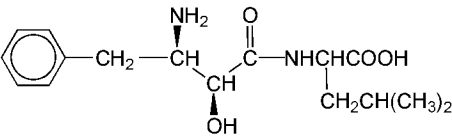
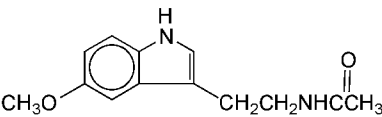


Table 2. Drugs Showing Thymomimetic Actions

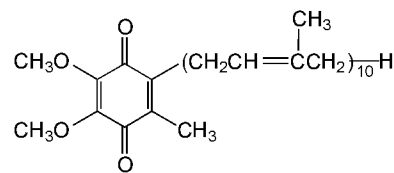
Name	Structure
sulfur-containing compounds	
levamisole ^a	
imuthiol ^b	
hypoxanthine derivatives	
isoprinosine ^c	
inosine pranobex ^{c,d}	
NPT 15392 ^c	

^a L(-) form of tetramisole [5036-02-2].
^b Diethyl dithiocarbamate, sodium salt; also known as Ditiocarb sodium.
^c Inosine complexed with 4-(acetylamino)benzoic acid and 1-(dimethylamino)-2-propanol (1:3:3);
molecular formula = C₁₀H₁₂N₄O₅·3C₉H₉NO₃·3C₅H₁₃NO.
^d CAS Registry Number = [36703-88-5].

Endogenous substances have been studied as immunoregulatory agents. Melatonin [73-31-4], the pineal neurohormone N-acetyl-5-methoxytryptamine, has been shown to antagonize the immunosuppressive effects of anxiety stress in mice, as measured by antibody production, thymus weight, and by the capacity of stressed- and evening-melatonin-treated mice to react against a lethal virus.

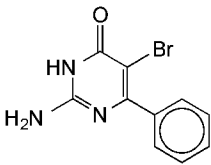


Melatonin thus could represent a new approach to the physiological control of stress and stress-related infectious diseases (48). The decline in immune function may partly depend on a deficiency of coenzyme Q, a group of closely related quinone compounds (ubiquinones) that participate in the mitochondrial electron transport chain (49). Concentrations of coenzyme Q (specifically coenzyme Q₁₀) appear to decline with age in several organs, most notably the thymus.



Administration of coenzyme Q₁₀ [60684-33-5] has been reported to have an adjuvant effect on humoral responses in mice, and to protect them from viral- and carcinogen-induced tumor formation. A decline in tissue and serum glutathione content and glutathione-metabolizing enzymes with age has been implicated in the increased susceptibility to infectious diseases and cancer that occurs with advancing age. However, a recent study showed that while the immune responsiveness of splenic lymphocytes in mice did decline with age, the intracellular level of glutathione [70-18-8] did not decline (50). Nevertheless, raising intracellular levels of glutathione did increase the immune responsiveness of both young and old lymphocytes. Glutathione is the tripeptide γ-Glu-Cys-Gly.

Natural killer (NK) cells and macrophages play an important role in host defense against a variety of pathogenic challenges including viruses, bacteria, parasites, and cancer cells. These cells of the immune system represent a more nonspecific first-line defense in that previous exposure to the antigen is not required for a rapid, active response. In addition, these cells, particularly macrophages, synthesize and secrete a number of important cytokines that are essential for proper immune regulation and function. A number of drugs have been developed to activate this arm of the immune response and to restore the diminished response in the aged. One such agent, broprimine [56741-95-8], C₈H₁₀BrN₃O, is a pyrimidinone that has shown good NK cell activation as measured by their enhanced ability to kill a susceptible tumor target (51).



This drug also is reported to activate macrophages, to induce polyclonal B-cell activation as well as enhance specific antibody production *in vivo*, and to induce the synthesis of interferon and interleukin 1 (52). The induction of these important cytokines (and others) largely accounts for the profile of biological activity displayed by the pyrimidinones. Broprimine is currently in clinical evaluation for cancer, arthritis, and immunorestitution in AIDS patients.

Another class of compounds that has been found to stimulate nonspecific, as well as some specific immune responses, is the 8-substituted guanosines (Fig. 1). Most notable examples include 8-bromo- [4016-63-1] and 8-mercaptoguanosine [26001-38-7], and 7-methyl-8-oxoguanosine. A sulfur analogue, 7-thia-8-oxoguanosine, has also recently been reported (53). These agents exhibit a somewhat similar biological profile to that of the pyrimidinones in that they stimulate interferon and IL-1 production, show broad-spectrum antiviral activity *in vivo* (53,54), and activate B-cells, NK cells, and macrophages. 7-Thia-8-oxoguanosine appears to be the most potent of the guanosines. Although the detailed mechanism of action whereby these guanosines activate the immune cells is not fully clear, there is some evidence to suggest that cellular activation occurs via the interaction of the drugs with guanine nucleotide binding proteins (G-proteins) (55,56). These pyrimidinones and guanosines represent a promising group of potential immunotherapeutic agents for the restoration of immune function in the aged as well as for the treatment of a variety of maladies via immune potentiation.

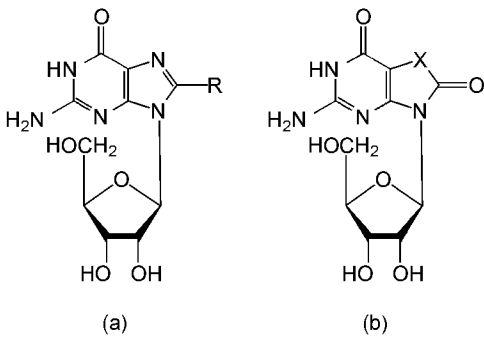


Fig. 1. 8-Substituted guanosines. (a) R = Br, 8-bromoguanosine (C₁₀H₁₂BrN₅O₅); R = SH, 8-mercaptoguanosine (C₁₀H₁₃N₅O₅S). (b) X = NCH₃, 7-methyl-8-oxoguanosine, C₁₁H₁₅N₅O₅; X = S, 7-thia-8-oxoguanosine (C₁₀H₁₂N₄O₅S).

The transmembrane signaling component of cellular activation has been an area of recent intense research interest. A report on the reduced proliferation of T-cells in aged humans indicated that the age-related defect in proliferation was mainly in the CD8⁺ (T-suppressor) cells and that it was predominantly in the CD4⁺ (T-helper) subset that decreases in transmembrane signaling were observed (57). This suggests that the reduced proliferation of T-cells from older donors is not related to transmembrane signal transduction. Indeed, one or more postsignal transduction events appear to be a more likely component involved in reduced T-cell proliferation in the aged. Certain thiol compounds have been shown to enhance the T-cell-dependent immune response of mice *in vivo* and the proliferation of T-cells *in vitro*. The magnitude of augmentation is often greater in old than young mice. T-cell responsiveness to IL-2 in the presence of 2-mercaptoethanol [60-24-2] was studied with respect to IL-2 synthesis *in vitro*, IL-2/IL-2 receptor binding interaction, and translocation of protein kinase C (PKC) from the cytosol to the membrane in cells from young and old mice. Results showed that 2-mercaptoethanol did not preferentially enhance IL-2 secretion or binding in cells from old or young mice, but it did preferentially augment the magnitude of PKC translocation in old versus young cells. This suggests that the metabolic event involved in PKC translocation is vulnerable to aging (58), an event which is a postsignal transduction event.

The interactions between nutrition and immunity have been the subject of much investigation and have been reviewed (59). It is now recognized that even mild deficiencies involving protein-calorie malnutrition and those involving single nutrients are associated with impaired immune responses. For example, mild deficiencies of vitamin A or zinc reduce cell-mediated immunity and a mild deficiency of iron decreases oxidative metabolic burst inside polymorphonuclear leucocytes. In one study, the oral administration of moderate amounts of zinc to subjects over 70 years of age for one month was associated with an increase in the number of circulating T-cells, cell-mediated immunity to several antigens, and serum immunoglobulin response to tetanus toxoid (60). However, large doses of "essential" nutrients (ie, zinc) may have a deleterious effect on the immune system (61). Corrections of deficiencies of iron, zinc, vitamins C, E, and B complex are associated with improved immune responses in the elderly (59) (see VITAMINS).

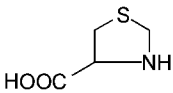
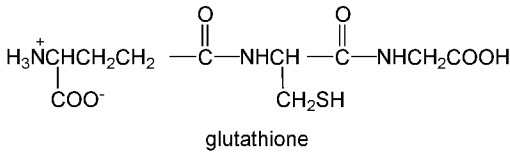
Finally, in another study related to nutrition and the immune response in the aged, old mice were given oral doses of two amino acids (qv), lysine and arginine. The treated mice showed evidences of recovered mitogenic responsiveness, expression of T-cell markers, and production of thymic serum factor (thymulin). The effect of the amino acid combination, sold commercially as Neoiodarsolo, seems to consist mainly of the reactivation of the

endocrine activity of the thymus. Similar results have been achieved in old humans. Thus it appears that the age-dependent decline of thymic hormonal activity is not an intrinsic and irreversible event and that some nutritional intervention, such as amino acid treatment, likely through the activation of the neuroendocrine network, may result in endogenous production of thymic hormones (62).

General Considerations

A number of agents have been studied for their effects on processes which are thought to be important factors in aging. One hypothesis suggests that an intracellular zinc deficiency may be a primary cause of the aging process (63) since zinc-metalloenzymes play an important role in many aspects of cellular metabolism. A zinc deficiency could result in malproduction of proteins and an accumulation of useless or toxic materials. However, apart from the immune response studies, no therapeutic trials have been conducted to evaluate this hypothesis.

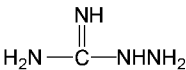
Antioxidants (qv) and free-radical scavengers have occupied a prominent place in modern antiaging research. A few of the studies are reviewed here. The endogenous substance, glutathione [70-18-8] (GSH), has been a topic of interest in aging research. GSH functions in detoxication during radical-induced injury in certain pathological and toxicological conditions. It protects against oxidative damage in systems that scavenge radicals, eliminate lipid peroxidation products, preserve thiol-disulfide status of proteins, and repair oxidant damage. Evidence indicates that GSH is a primary component of physiological systems to protect against oxidant and free-radical-mediated cell injury (64). The decrease in tissue GSH concentrations in different senescent organisms gave rise to the hypothesis that a GSH deficiency is a biochemical cause of the aging process.



4-thiazolidinecarboxylic acid

Correction of the deficiency should therefore result in increased life span. To test this idea, adult mosquitos were fed magnesium 4-thiazolidinecarboxylate [18805-09-9] and their GSH levels and life spans were determined. The GSH levels increased 50 –100% and the median life span increased 30–38% over control values. The responses were specific for the 4-thiazolidinecarboxylic acid moiety, because magnesium chloride had no effect (65). Another antioxidant, 2-mercaptoethanol, HSCH₂CH₂OH, has been shown in several studies to increase the life span of laboratory animals. The beneficial effects may be due to a more rapid turnover time in total body protein and an increase in the proportion of polyunsaturated fatty acids in the liver lipids of the treated group (66). In another study, the addition of the antioxidant sodium hypophosphite [7681-53-0] NaH₂PO₂, to the diets of flies increased their life spans possibly as a result of slowing the age-related decline in the enzyme activity of ATPase and catalase as well as acting as a free-radical scavenger (67).

Age-associated increases in collagen cross-linking and accumulation of advanced glycosylation products may contribute to the development of the typical pathology of aging and diabetes. Aminoguanidine [79-17-4], a nucleophilic hydrazine compound, was shown to prevent both the formation of fluorescent advanced nonenzymatic glycoylation products and of glucose-derived cross-links of arterial wall collagen in rats *in vitro* and *in vivo* (68).



These results suggest a potential role for aminoguanidine in the future treatment of chronic diabetes complications.

Hormonal effects on the aging process have been areas of current interest. The intricacies of the interaction of the various hormones are undoubtedly involved in the aging process and hence these hormones could be called antiaging agents. Both androgens and estrogens have been studied. Low level estrogen replacement therapy (ERT) has been used to treat postmenopausal women.

Various estimations indicate that nearly twenty million women in America suffer osteoporotic problems. The physiological changes that take place are certainly forms of aging. In one five-year study where ERT compliance was carefully monitored, the bone mineral density increased regardless of the length of treatment or the patient's age when therapy commenced (69).

Reports have appeared in the literature of the use of human growth hormone in older men. It has been proposed that a reduction in growth hormone in old age is responsible for increased adipose tissue, loss of lean body mass, and thinning of skin. Current studies conducted on older men indicate the hormone reverses these effects. In the parameters studied the patients resembled those of persons 10 –20 years younger (70).

Availability of larger quantities of other hormones utilizing current biotechnology could reveal several other interesting antiaging agents including hormones, hormone analogues, and various receptor binding and activating substances.

Applications

Although significant advances have been made during the last decade in the development of agents for the treatment of age-related disorders (ie, immune restoration, enhancement of memory, and cognitive function), no convincing clinical data is yet available indicating effective pharmacological (or nutritional) intervention in the fundamental aging process itself. As basic understanding of the aging process advances at the molecular level, such data may allow a formulation of effective agents for the therapeutic modulation of these processes.

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ANTIALLERGIC AGENTS.

See ANTIASTHMATIC AGENTS.

ANTIALLERGY AGENTS.

See HISTAMINE AND HISTAMINE ANTAGONISTS.

ANTIANEMIA PREPARATIONS.

See IRON COMPOUNDS; PHARMACEUTICALS; VITAMINS.

ANTIANGINAL AGENTS.

See CARDIOVASCULAR AGENTS.

ANTIANXIETY AGENTS.

See PSYCHOPHARMACOLOGICAL AGENTS.

ANTIARRYTHMIC DRUGS.

See CARDIOVASCULAR AGENTS.

ANTIASTHMATIC AGENTS

Asthma is an extremely complex condition characterized by variable and reversible airways obstruction combined with nonspecific bronchial hypersensitivity (1–3). The cause of asthma, which is not always readily diagnosed (4), remains unknown. Days, if not weeks, are needed to document the spontaneous reversal of the airways obstruction in some patients. Asthmatics experience both an immediate hypersensitivity response and a delayed late-phase reaction, each mediated by a different pathway. Chronic asthma has come to be viewed as an inflammatory disease (5). The late-phase reaction plays a key role in inducing and maintaining the inflammatory state which in turn is thought to induce the bronchial hyperresponsiveness (6). The airways obstruction results from both contraction of airways smooth muscle and excessive bronchial edema. Edema, a characteristic of inflammatory states, is accompanied, in this case, by the formation of a viscous mucus which can completely block the small airways.

Asthma affects 3–5% of the population and is one of the most common chronic illnesses (7–9). Both the frequency and severity of asthma appear to be increasing (10–13). Acute, severe asthma has the potential to be fatal. The disease may first appear in childhood and individuals so affected can suffer recurrent episodes throughout their lives or they may "outgrow" the condition at puberty. On the other hand, there is also adult-onset asthma. These people show no symptoms as children or as young adults, but suddenly develop symptoms later in life. There have been many reports of bronchial infections preceding the appearance of asthma. However it is not known whether these infections contributed to the development of the disease or whether individuals who are already predisposed to asthma are more likely to experience bronchospasms as a result of a bronchial infection (14).

Clinically, there are several ways of classifying asthma and treatment varies depending upon the classification. Extrinsic asthma, also called allergic asthma, is experienced by adults and, most commonly, by children. In extrinsic asthma it is possible to demonstrate specific causal agents, usually antigens, eg, animal danders, foods, drugs, house dust, pollens, or mold spores. Atopic extrinsic asthmatics usually have elevated levels of circulating immunoglobulin E (IgE), have a family history of inherited allergies (atopy), and commonly show other allergic symptoms such as rhinitis, or have a history of eczema (15). However, especially in occupation-induced asthma, irritants may act as the allergenic agent and IgE does not appear to be involved in some nonatopic extrinsic asthmatics.

Intrinsic asthma, also called idiopathic asthma, usually develops in adulthood. In intrinsic asthma allergic factors are not demonstrable. Episodes of intrinsic asthma may be triggered by a variety of stimuli, eg, emotional state, exposure to cold air, or inert dusts. Both intrinsic and extrinsic asthmatics can be prone to exercise-induced attacks. Individuals who experience a combination of extrinsic and intrinsic asthmatic reactions have mixed asthma. Status asthmaticus refers to an especially acute life-threatening asthma attack which is resistant to normal treatments and which may require hospitalization in order to stabilize the patient.

Current asthma treatments are not curative and historically have relied on pharmacologic intervention with bronchodilators (Fig. 1) (16) to prevent or relieve the symptoms of asthma. More recently the focal points of both treatment and research efforts have shifted from bronchodilators to agents which reduce the underlying inflammatory state (5,6,17). Management of extrinsic asthma usually includes manipulation of the patient's environment to minimize or completely eliminate the causal agent. This can be especially beneficial in occupationally induced asthma. Treatment of extrinsic asthmatics may also include hyposensitization, or desensitization, by exposure to small and increasing amounts of the known antigen. Although hyposensitization is widely used by allergists for the treatment of allergic rhinitis, its use and potential benefit in the treatment of strictly defined asthma remains controversial (18–20). The cascade of events involved in the asthmatic response and potential points for pharmacologic intervention are shown in Figure 1.

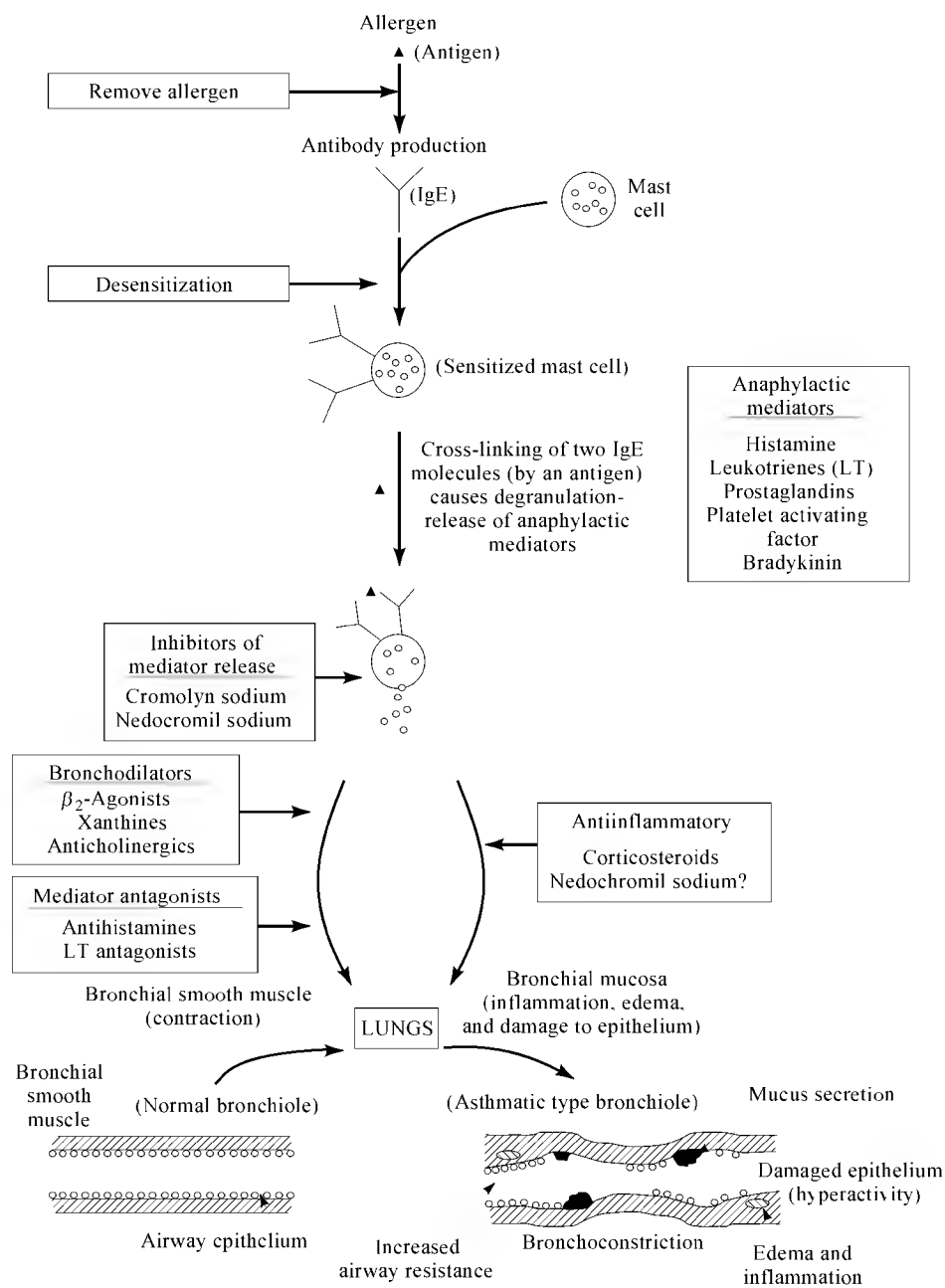


Fig. 1. Schematic diagram showing possible sites of action of antiasthmatic drugs.

The order of preference of drug treatment varies from country to country (21,22) (Table 1). In part this difference reflects the lack of a "magic bullet" for the treatment of asthma. However, this difference may also be explained by differences in marketing approval. Some agents are not yet available in the United States and the exposure of U.S. physicians to some of the newer inhalation formulations has been limited. However, the use of inhaled, rather than oral, agents has begun to increase in the United States (23,24) as indicated by the changes in the market for prescription antiasthmatic drugs. In the period from 1984 to 1989 the share of new prescriptions for inhaled β_2 -agonists increased from 18% to 26%, whereas that for oral xanthines dropped from 39% to 27% (25).

Table 1. Order of Preference for First Choice Antiasthmatic Agent Maintenance Therapy

	Order of preference		1989 U.S. market share, % ^c
	U.S. ^a	UK ^b	
oral xanthines	1	4	~27
inhaled β_2 -agonist	2	1	~26
oral β_2 -agonist	3		~18
inhaled steroid	4	2	~18
inhaled inhibitor of mediator release	5	3	~5

^a Ref. 21.

^b Ref. 22.

^c Ref. 25.

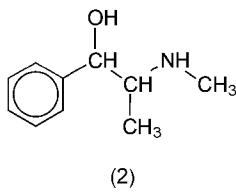
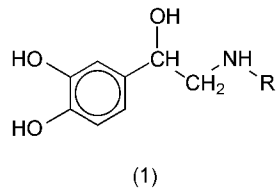
Courtesy of IMS International, a company of Dun & Bradstreet Corporation.

Improvements in asthma treatment include the development of more effective, safer formulations of known drugs. The aerosol administration of β_2 -agonists or corticosteroids results in a decrease in side effects. Also, the use of reliable sustained release formulations has revolutionized the use of oral xanthines which have a very narrow therapeutic index (see CONTROLLED RELEASE TECHNOLOGY). For many individuals, asthma symptoms tend to worsen at night and the inhaled bronchodilators do not usually last through an entire night's sleep (26,27).

β -Adrenergic Stimulants

β_2 -Agonists are widely used in the symptomatic treatment of asthma. Although both oral and aerosol formulations of these bronchodilators have been available for many years, advances have occurred in delivery technology with the development of dry powder aerosols (qv) (see DRUG DELIVERY SYSTEMS) (28). The ease of usage of these breath-activated systems has improved patient compliance and therapeutic response. There are several detailed reviews on β_2 -agonist therapy of bronchial asthma (29–31), and on the structure-activity relationships of this class of drugs (32).

The modern usage of β_2 -agonists for the treatment of asthma dates to 1903 when the effect of injected epinephrine [51-43-4] (adrenaline) $C_9H_{13}NO_3$, (1, R = CH_3) was investigated (see EPINEPHRINE AND NOREPINEPHRINE) (33). As in some other modern treatments, eg, xanthines and anticholinergics, the roots of β_2 -agonist therapy for asthma can be found in historical records which document the use of herbal extracts containing ephedrine [299-42-3], $C_{10}H_{15}NO$, (2) as bronchodilators. Epinephrine and ephedrine are structurally related to the catecholamine norepinephrine [51-41-2], $C_8H_{11}NO_3$, (1, R = H), a neurotransmitter of the adrenergic nervous system (see NEUROREGULATORS).



Endogenous catecholamines have an extremely short half-life and reuptake into sympathetic nerve storage vesicles is the main mechanism for removing norepinephrine from circulation. To some degree reuptake also occurs with epinephrine. This process is relatively selective, however, and does not readily take place with nonnaturally occurring catecholamines. Catecholamines that escape reuptake are rapidly catabolized by two widely distributed enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). The former transfers a methyl group to the 3-hydroxy of catecholamines. The resultant 3-methoxy compounds have no adrenergic agonist activity and in some cases may be adrenergic antagonists. MAO is less discriminatory, cleaving the carbon–nitrogen bond of primary and secondary amines with concomitant oxidation of the carbon atom.

Ephedrine, which is not a catecholamine, has weak oral activity as a bronchodilator and although it has some direct action at adrenergic receptors, its predominant mode of action is by displacing norepinephrine from storage vesicles. β_2 -Agonists which are in use or are under investigation are the result of quests for improved selectivity, retention of potency, oral activity, and longer duration of action.

The adrenergic nervous system is one of the two main branches of the autonomic nervous system (34), which regulates the so-called automatic functions of the body, eg, the actions of various organs such as the lungs and heart. The other main branch of the autonomic nervous system is called the cholinergic nervous system and it has acetylcholine [51-84-3], $CH_3COO(CH_2)_2N(CH_3)^+$, (see CHOLINE; ENZYME INHIBITION) as a neurotransmitter. More recently, a third branch to the autonomic nervous system has been identified in human (35) and animal airways (36,37). In this nonadrenergic, noncholinergic nervous system both the neurotransmitter and the importance in lung function are in dispute (38). The adrenergic and cholinergic nervous systems often act in opposition to one another (34).

Division of the receptors in the adrenergic nervous system into two classes (α and β) was proposed in 1948 (39) when a difference in the rank order of potency of epinephrine (1, R = CH_3), norepinephrine (1, R = H), and isoproterenol [7683-59-2], $C_{11}H_{17}NO_3$, (1, R = $CH(CH_3)_2$) was noted to depend on the organ examined. Further subdivision into groups β_1 and β_2 was proposed in 1967 (40). Both types of β -adrenoceptors are found throughout the body. One of the more significant roles for β_1 -receptors is in cardiac tissues where they mediate contraction. Although the effect of triggering β_2 -receptors is tissue-dependent, stimulating those found in bronchial and vascular smooth muscle induces relaxation (Fig. 2). Stimulating the adrenergic receptor results in activation of adenylate cyclase which in turn catalyzes production of cyclic-3',5'-adenosine monophosphate (cyclic AMP). The cyclic AMP then acts as a second messenger activating a protein kinase which selectively phosphorylates myosin kinase resulting in inhibition of calcium-dependent smooth muscle contraction. Also, activation of β_2 -adrenoceptors results in the inhibition of cholinergic neurotransmission in human airways (41) and this too should cause smooth muscle relaxation.

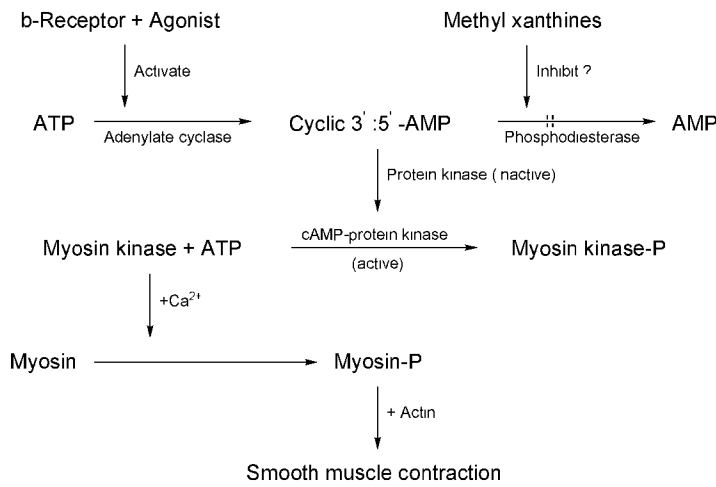


Fig. 2. Proposed mechanism of inhibition of smooth muscle contraction by β_2 -agonists, where AMP is adenosine monophosphate, cAMP is cyclic-3:5' adenosine monophosphate, ATP is adenosine triphosphate, and -P is an attached phosphate.

Elevation of cyclic AMP levels is also known to inhibit the release of inflammatory and contractile mediators from mast cells (42). The good clinical efficacy of β_2 -agonists may be related to this action because some members of this class of drugs inhibit mediator release at the same concentrations at which they relax smooth muscle (43). In contrast to their effectiveness against immediate bronchoconstriction, β_2 -agonists do not inhibit the late asthmatic

response or reverse bronchial hyperreactivity (44,45).

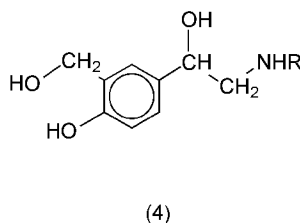
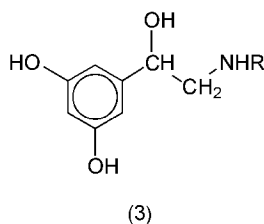
Because of the widespread nature of adrenoceptors, nonselective β -agonists can produce many undesirable side effects. Therefore, before adrenergic agonists could become widely used in the treatment of asthma, some selectivity in action was needed. Whereas epinephrine and ephedrine have significant agonist activity at both α and β adrenoceptors, isoproterenol is a selective agonist at the β -receptor (39). However, isoproterenol does not distinguish between the β_1 and β_2 receptors and it is not active orally.

Aerosol administration of isoproterenol produces a prompt (2–5 minutes) intense bronchodilatation of relatively short (1 h) duration. The lack of β_2 -selectivity leads, in many cases, to tachycardia and blood pressure elevation. Also, use of isoproterenol, like all other known β -agonists, results in a down-regulation, or desensitization, of β -adrenergic receptors. This desensitization is only partial, and after time (depending on dose, patient, and agent), a stable, less responsive state is achieved in which β -agonists remain effective. Isoproterenol has been widely used for many years.

A significant advance in β -agonist therapy occurred with the discovery of metaproterenol [586-06-1], $C_{11}H_{17}NO_3$, (3 R = $CH(CH_3)_2$). Replacing the catechol subgroup with a resorcinol unit results in a compound which is no longer susceptible to metabolism by COMT and therefore has a longer (4 h) duration of action. Metaproterenol has a selectivity profile that is similar to that of isoproterenol, but it is 10–40 times less potent *in vitro* (46). However, metaproterenol is active if given orally and, therapeutically, it is administered either orally or by aerosol. Better selectivity of action is achieved by the aerosol route, although large or frequently repeated aerosol doses may also cause side effects.

Changing the *N*-substituent of metaproterenol to a *tert*-butyl group gives rise to terbutaline [23031-25-6], $C_{12}H_{19}NO_3$, (3 R = $C(CH_3)_3$) (47), an orally active agent having a duration of action of from 6–7 h. The presence of a tertiary carbon alpha to the amine protects against the action of MAO. Also, it had been shown earlier for catecholamines that increasing the steric bulk around the nitrogen results in improved β_2 -selectivity (32). This finding carries over to the resorcinol series: terbutaline stimulates β_2 -receptors to a significantly greater extent than β_1 -receptors.

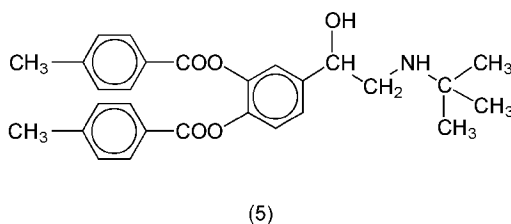
Terbutaline has about six times the selectivity of isoproterenol and is claimed to produce fewer side effects. Terbutaline inhibits the release of mediators from sensitized human lungs at clinically relevant concentrations (31), and has been shown to have a prophylactic effect in bronchial challenge studies in addition to being a bronchodilator. Also, nasal administration of fenoterol [13392-18-2], $C_{17}H_{21}NO_4$, (3, R = $CH(CH_3)CH_2C_4H_4OH$), a closely related β_2 -agonist, in clinical studies on the treatment of allergic rhinitis has clearly shown inhibition of release of allergic mediators (48,49). Both aerosol and oral formulations of terbutaline are in use, although examination of an oral slow-release formulation for use in nocturnal asthma revealed that patients preferred long-acting theophylline preparations because of the incidence of undesired side effects (50).

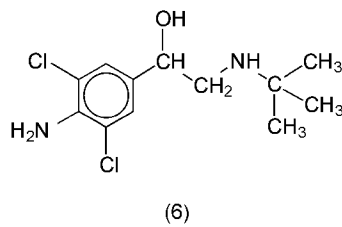


Variation of the substituents on the aromatic ring led to the discovery that the 3-hydroxy could be replaced with a variety of groups, eg, CH_2OH , $NHCH_3$, $NHCONH_2$, $NHS(O)_2CH_3$, that successfully mimic the electron donating and hydrogen bonding properties of the hydroxide moiety at the adrenergic receptor. The 3- CH_2OH analogue has been the most studied in this series of compounds. Albuterol [18559-94-9], $C_{13}H_{21}NO_3$, (4 R = $C(CH_3)_3$) also called salbutamol (51), is the most widely prescribed β_2 -agonist for either aerosol or oral administration both in the United States and worldwide.

Replacement of the hydroxy with CH_2OH results in resistance to both COMT and conjugation. Also, because the *tert*-butyl group confers resistance to MAO, albuterol is metabolically quite stable and animal studies have shown that it is excreted unchanged and as the phenolic glucuronide (31). *In vitro*, albuterol has been shown to inhibit mediator release and to have about 59 times the β_2/β_1 -selectivity of isoproterenol (32). In contrast, clinical studies using po albuterol reveal only a seven- to tenfold improvement in selectivity as compared to isoproterenol (52). Studies using aerosol administration show that albuterol has fewer side effects, more rapid onset, and at least the same duration of action (5 h) as the immediate release oral formulations. It is believed that the cardiac responses following oral administration result from an indirect reflex stimulation of cardiac output. This reflex results from the lowering in blood pressure that the β_2 -agonist induced relaxation of vascular smooth muscle produces. Because of this finding the preferred mode of administration of β_2 -agonists is by aerosol even with newer, more selective agents.

More recent research efforts have focused on the development of longer acting β -agonists which could be administered less frequently and be more efficacious in controlling nocturnal asthma. There are several agents currently under clinical evaluation. Bitolterol [30392-40-6], $C_{28}H_{31}NO_5$, (5) represents one approach to extending duration of action. It is a prodrug having no direct effect at adrenergic receptors; it must be hydrolyzed by esterases to the active phenolic agent. Bitolterol, presumably because of differential rates of hydrolysis, gives unpredictable bronchodilation if given orally (53). However it is hydrolyzed efficiently in the lung and an aerosol formulation of it has been compared, albeit unfavorably, with sustained release theophylline for control of nocturnal asthma (27).





Clenbuterol [37148-27-9], C₁₂H₁₈Cl₂N₂O, (6) (54), a nonphenolic analogue of terbutaline, is not susceptible to COMT or to conjugation. It has a long plasma half-life (20 h), but does not seem to differ in pharmacological half-life from albuterol (55).

Salmeterol [89365-50-4], C₂₅H₃₇NO₄, (4, R = (CH₂)₄ O(CH₂)₄ C H₃) (56), is a long-acting analogue of albuterol in which the amine substituent is a long lipophilic chain. Although the plasma half-life of salmeterol is the same as that of albuterol, salmeterol has a much longer (12 h) duration of action following aerosol administration and tests to determine its efficacy in nocturnal asthma are underway (55). *In vitro*, salmeterol is about five times as potent as salbutamol and also shows an unusually extended duration of action (57) which might result from exo-receptor binding (56).

Although β₂-agonists are useful in the treatment of asthma, the profiles would be improved if the bronchodilating effects could be further separated from the side effects. It is not clear how this could be accomplished, but it has been shown that a β₃-receptor exists in humans and other uncharacterized subclasses of receptors have also been postulated (58). The investigation of these other β-receptors could lead to more selective agents.

Xanthine Derivatives

For many years oral xanthines, shown in Table 2, were the preferred first-line treatment for asthma in the United States, and if the aerosol and oral formulations of β₂-agonists are considered separately, as they are in Table 1, this was still the case in 1989. Within this class of compounds theophylline (8), or one of its various salt forms, such as aminophylline [317-34-0] (theophylline: ethylenediamine::2:1), have been the predominant agents. Theophylline, 1,3-dimethylxanthine [58-55-9], is but one member of a class of naturally occurring alkaloids. Two more common alkaloids are theobromine (9), isomeric with theophylline and the principal alkaloid in cacao beans, and caffeine, (10), 1,3,7-Trimethylxanthine [58-08-2], found in coffee and tea.

Table 2. Xanthine and Xanthine Derivatives Used as Oral Antiasthmatic Agents

Chemical structure of a xanthine derivative showing the purine ring system with substituents R, R', and R''.

Compound	CAS Registry Number	Molecular formula	Structure number	R	R'	R''
xanthine	[69-89-6]	C ₅ H ₄ N ₄ O ₂	(7)	H	H	H
theophylline	[58-55-9]	C ₇ H ₈ N ₄ O ₂	(8)	CH ₃	CH ₃	H
theobromine	[83-67-0]	C ₇ H ₈ N ₄ O ₂	(9)	H	CH ₃	CH ₃
caffeine	[58-08-2]	C ₈ H ₁₀ N ₄ O ₂	(10)	CH ₃	CH ₃	CH ₃
enprofylline	[41078-02-8]	C ₈ H ₁₀ N ₄ O ₂	(11)	H	<i>n</i> -C ₃ H ₇	H

The bronchodilating effect of caffeine has been recognized for hundreds of years. In the western world the first description of a caffeine preparation for asthma was made in 1859 (59) by a Scottish physician who recommended strong black coffee as a bronchodilator. In many parts of the world, however, use of xanthines is less frequent than in the United States.

Historically, the use of xanthines has been hampered by poor aqueous solubility, rapid but highly variable metabolism, and the existance of a low therapeutic index. Solubility problems were partially solved by the preparation of various salt forms, eg, aminophylline. However, it was since recognized that the added base in aminophylline only increases solubility by increasing pH and thus does not affect the rate of absorption from the gut (65). Thus, in more recent medical practice, theophylline is commonly dispensed in anhydrous form and aminophylline is only recommended for iv administration.

The development of easy-to-use assays for determining theophylline blood levels afforded a handle on maintenance of effective but nontoxic levels. The relatively good availability of such assays in the United States probably contributed to the historical preference for theophylline treatment by U.S. physicians. Careful titration of the dose must be done on a patient-by-patient basis because individual rates of metabolism vary widely. Most (~85%) of an oral dose of theophylline is metabolized by liver microsomal enzymes. As a result many drugs, eg, cimetidine [51481-61-9], anticonvulsants, or conditions, eg, fever, cigarette smoking, liver disease, which affect liver function alter theophylline blood levels.

Common side effects of theophylline therapy include headache, dyspepsia, and nausea. More serious side effects such as lethal seizures or cardiac arrythmias can occur if blood levels are too high. Many derivatives of theophylline have been prepared in an effort to discover an analogue without these limitations (60,61). However, the most universal solution has resulted from the development of reliable sustained release formulations. This technology limits the peaks and valleys in serum blood levels that occur with frequent dosing of immediate release formulations. Controlled release addresses the problems inherent in a drug which is rapidly metabolized but which is toxic at levels (>20 γg mL) that are only slightly higher than the therapeutically efficacious ones (10–20 μg mL). Furthermore, such once-a-day formulations taken just before bedtime have proven especially beneficial in the control of nocturnal asthma (27,50,62).

The effectiveness of theophylline in the treatment of asthma seems to result from a combination of biological properties which are not clearly understood (63). Detailed discussions of the possible role of xanthines in asthma may be found in references 64–66.

The effects of xanthine alkyl substitution on bronchodilation have been summarized as follows (60,61): N₁ alkylation is essential for adenosine antagonism, bronchodilator and toxic potency may increase; N₃ alkylation is essential for increased bronchodilator potency, toxicity may increase; N₇ alkylation results in decreased bronchodilator and toxic potency; C₈ alkylation has no effect on bronchodilator potency, but toxic potency and adenosine antagonism may increase; and N₉ alkylation results in general loss of potency.

Theophylline's predominant mode of action appears to be bronchodilation. However, it has also been shown that prophylactic administration of theophylline provides some protection from asthma attacks and suppresses the late-phase response (67,68). Some researchers believe that at therapeutic serum concentrations theophylline may inhibit the development of airway inflammation (69). There are conflicting reports on the effect of theophylline on allergen-induced bronchial hyperresponsiveness: some clinical studies report a reduction in hyper-responsiveness, others do not (69,70). Theophylline clearly does not reverse the general bronchial hyperresponsiveness over the course of long-term therapy (71). Because of the relationship between

hyperresponsiveness and inflammation (Fig. 1), these findings argue against theophylline having a significant antiinflammatory component. Initially, it was believed that the ability of xanthines phosphodiesterase (PDE) led to bronchodilation (Fig. 2). One significant flaw in this proposal is that the concentration of theophylline needed to significantly inhibit PDE *in vitro* is higher than the therapeutically useful serum values (72). It is possible that concentration of theophylline in airways smooth muscle occurs, but there is no support for this idea from tissue distribution studies. Furthermore, other potent PDE inhibitors such as dipyridamole [58-32-2] are not bronchodilators (73). Finally, although clinical studies have shown that neither po nor continuous iv theophylline has a direct effect on circulating cyclic AMP levels (74,75), one study has shown that iv theophylline significant potentiates the increase in cyclic AMP levels induced by isoproterenol (74).

An alternative mechanism which has more recently been suggested is antagonism by theophylline of adenosine receptors. This is a well-documented effect which has been blamed for causing many of the theophylline side effects. Adenosine has a bronchoconstrictor effect when given by inhalation to asthmatics but not when given to controls (76). Also, asthmatics release adenosine into the circulation following antigen-induced bronchoconstriction (77). Therefore, it may be relevant that theophylline is an antagonist of adenosine at therapeutically useful concentrations (78). Arguing against this theory is the fact that enprofylline (3-propylxanthine [41078-02-8]), (11) is simultaneously claimed as a more potent bronchodilator than theophylline and not being an adenosine antagonist (67,79,80). Furthermore, theophylline relaxes airways smooth muscle *in vitro* probably independently of adenosine antagonism because significant concentrations of adenosine should not be present under *in vitro* conditions.

Although the benefit of theophylline treatment in asthma is without question, its use is decreasing as a result of the introduction of other effective drugs which do not have the same potential for serious side effects. It is as yet unclear whether enprofylline is a better agent or whether better drug design will require a better understanding of theophylline's mechanism of action. A theophyllinelike agent, lacking the side effects profile, would clearly be advantageous in the treatment of asthma.

Steroids

Steroids are widely used for the preventative treatment of asthma. Especially useful in the management of severe cases, their usage appears to be increasing. However, they have had a checkered history in asthma treatment. Shortly after the first synthetic corticosteroids became available, po cortisone (12) (Table 3) was tried as an antiasthmatic agent and showed remarkable success (81). However, within a few years the number and severity of side effects reported from the systemic administration of nonselective corticosteroids was deemed unacceptable (82–84). In an effort to reduce systemic side effects, treatment of asthmatics with inhaled cortisone was explored (85). Although this therapy was successful, steroid-induced side effects such as adrenal suppression and retention of both sodium and water still occurred, resulting in the long held view that whereas corticosteroids are effective antiasthmatic agents, they should only be used when all other therapy fails to control the disease.

Table 3. Steroids Used as Antiasthmatic Agents

Name	CAS Registry Number	Molecular formula	Structure number	Structure
cortisone	[53-06-5]	C ₂₁ H ₂₈ O ₅	(12)	
prednisone	[53-03-2]	C ₂₁ H ₂₆ O ₅	(13)	
beclomethasone dipropionate	[5534-09-8]	C ₂₂ H ₂₉ ClO ₅	(14)	
budesonide	[51333-22-3]	C ₂₅ H ₃₄ O	(15)	

Resurgent interest in the use of steroids for the treatment of asthma has been prompted by several developments. First, came the discovery of steroids such as prednisone (13), beclomethasone dipropionate (14), and budesonide (15). These newer, more selective, compounds successfully separate glucocorticoid (anti-inflammatory) and mineralocorticoid (electrolyte regulation) activities and do not suppress serum hydrocortisone. Both beclomethasone dipropionate and budesonide were initially developed as topical agents for dermatological indications. Later they were reformulated using aerosol delivery systems to produce antiasthmatic agents having good efficacy which do not produce most of the side effects found with oral steroids (86,87,88). In part, the selectivity of both of these agents derives from the ability to get into the circulatory system where they are rapidly converted into less active metabolites that do not behave as systemic glucocorticoids. Steroid usage has increased because of the identification of asthma as an inflammatory disease. Thus aerosolized antiinflammatory steroids are often used for first-line asthma treatment (5,6).

Although the mechanism of glucocorticosteriod action in bronchial asthma is not fully understood, various possibilities have been discussed in

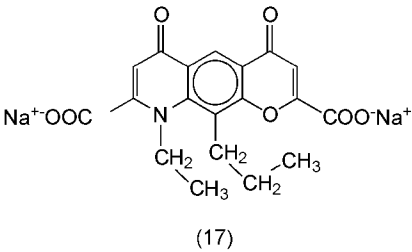
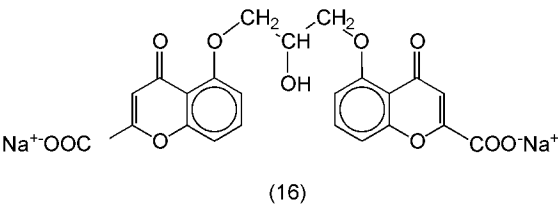
depth (89,90). The time course of action of steroids is slower than that of β_2 -agonists or theophylline and therefore steroids are not considered to be bronchodilators. It is known that steroids bind to cytosolic receptors. The steroid-receptor complex then enters the cell nucleus where the complex acts at specific sites and affects protein synthesis. The effect is to reduce the inflammatory response as well as the concentration of bronchoconstricting mediators. In addition, glucocorticoid treatment is known to reverse β_2 -agonist induced adrenergic subsensitivity and to increase the number of β_2 -adrenergic receptors in lung cells (91). The resultant increase in sensitivity to the natural circulating levels of norepinephrine could help induce bronchorelaxation.

Single dose or short-term treatment with aerosolized steroids inhibits both the late asthmatic response and allergen-induced bronchial hyperresponsiveness (45,92). However it does not affect the early asthmatic response nor does it induce bronchodilation (45,92). Long-term treatment with steroids protects against both the early and late asthmatic responses and also reduces bronchial hyperresponsiveness (44,71,86,93). Over time, the airways relax (dilate) and measures of airway function, such as forced expiratory volume in one second (FEV₁), gradually return to almost normal levels.

Aerosolized steroids clearly play an important role in the present-day management of asthma (87). They are reasonably safe and work best when taken prophylactically. Patient compliance, however, remains a significant problem. In part this problem is typical of any aerosolized agent. But in the case of steroids, the problem is exacerbated because a patient needs to take the steroids (especially prednisone) are the antiasthmatic agents of last resort and are widely used to treat status asthmaticus. An agent that could mimic the actions of steroids but which would work faster and or without side effects might be the ideal antiasthmatic agent.

Inhibitors of Mediator Release

Whereas disodium chromoglycate [15826-37-6] (DSCG), C₂₃H₁₄Na₂O₁₁, (16) enjoys some modest success as a preventative antiasthmatic agent, it has never achieved the same level of popularity in the United States as it has in other markets, such as in the United Kingdom. Its properties have been covered in detail in several reviews (94,95). DSCG was discovered by testing by an allergic man without the support of animal models (94,96). This uncommon approach is now viewed as unacceptable. DSCG has been unique in its class for many years, partly because early tests designed to determine the mode of action showed that DSCG is not an antagonist of any of the known mediators of asthma nor does it induce bronchodilation (95).



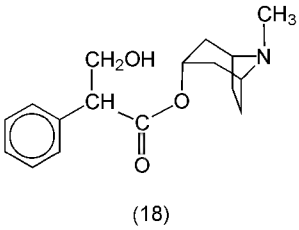
To aid in both the understanding of DSCG's effective mechanism and the discovery of an active analogue, animal models were developed (97). It was believed that DSCG's mode of action is by stabilization of mast cells and inhibition of mediators' release (42,98). The tremendous effort expended by the pharmaceutical industry initially resulted in failure. These investigations have been reviewed in depth (97), and it is now believed that improper disease models were employed (99,100). These early models measured the stabilizing effect of the test agents on connective tissue mast cells. Newer models have focused on mucosal (lung) mast cells and a more recent proposal is that DSCG and a related compound, nedocromil sodium [69049-74-7], C₁₉H₁₅NNa₂O₇, (17), both inhibit the effect of sensory nerve activation, thereby interfering with bronchoconstriction (101).

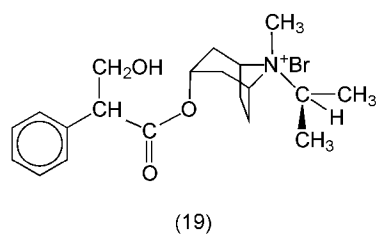
DSCG is very poorly absorbed following oral dosing and is therefore administered by aerosol inhalation, four times a day (94,95). Metabolism is minimal: DSCG is excreted mostly as unchanged drug. Thus, although it is considered one of the safest available antiasthmatic agents, it is not a cure-all and seems to work best as an adjunct to other therapy, allowing a reduction in the dosage of the other agents (94). Clinical studies show that DSCG offers no protection if administered following antigen challenge (94,95), but if administered prophylactically, it protects both extrinsic and intrinsic asthmatics (94,102,103). DSCG is uniquely effective against both the early and late-phase asthmatic responses; it also protects against exercise-induced asthma (45,104,105). The effect of DSCG on nonspecific bronchial hyperreactivity is not at all clear; clinical studies have produced conflicting reports (45,104–106).

With the shift in preference to aerosolized agents, nedocromil sodium (17) has been introduced as a follow-up agent to DSCG (16) (107–109). Nedocromil sodium, structurally distinct from DSCG, is significantly more potent in humans, and can be administered twice daily. Like DSCG, it is administered only via an aerosol, is not significantly metabolized, and is excreted as unchanged drug. The rate limiting step for the duration of action seems to be absorption. A clinical trial has shown that, if given four times a day at 4 mg per dose, nedocromil sodium is comparable with, and equivalent to, inhaled beclomethasone dipropionate (14) in nearly all parameters (110).

Anticholinergic Agents

At this writing anticholinergic agents are not widely used for the symptomatic treatment of asthma, although compounds such as atropine [51-55-8], C₁₇H₂₃NO₃, (18) have been used for centuries (111). Inhalation of the smoke produced by burning herbal mixtures, such as *Datura Stramonium*, provided bronchodilation and relief from some of the symptoms of asthma. The major active component in these preparations was atropine or other closely related alkaloids (qv).





The beneficial effect of anticholinergics in asthma relies upon bronchial smooth muscle exhibiting a cholinergically mediated tone (resting state tension) (112,113). Receptors in the cholinergic nervous system are divided into two main classes, muscarinic (M) and nicotinic (113). Anticholinergic agents exert their bronchodilating effect by blocking the muscarinic-receptors found in bronchial smooth muscle. This blockade inhibits the normal cholinergic-induced tone. In addition, it has been shown that cholinergic receptor stimulation results in inhibition of adenylate cyclase, thereby reducing cyclic AMP levels (114). Blockade of this effect should result in indirect bronchodilatation (Fig. 2). Although atropine is effective in preventing exercise-induced asthma (103), it and other anticholinergic agents have no effect on bronchial hyperresponsiveness, the release of other mediators, or on the inflammatory process (115,116). Significant dose related side-effects such as blurred vision, dry mouth, and inhibition of gastric motility occur. These side effects result from systematic distribution of the drugs, including penetration into the central nervous system and their widespread antagonism of other muscarinic receptors.

Ipratropium bromide [22254-24-6], C₂₀H₃₀BrNO₃, (19) (115) is an example of a newer anticholinergic agent. This isopropyl quarternary salt derivative of atropine is not lipid soluble or well-absorbed through the gut, nor does it readily cross the blood-brain barrier. Using aerosol administration, this agent has a much lower incidence of side effects. Ipratropium bromide has gained limited acceptance as an antiasthmatic agent and seems to be more useful in patient populations that show limited response to B₂-adrenergic agonists (117). Clinical studies suggest that a synergistic effect may result from the co-administration of a B₂-agonist and an anticholinergic agent (117,118).

Research efforts on anticholinergic agents have been influenced by the finding that muscarinic-receptors can be divided into subtypes: M₁, M₂, and M₃ (119–121). It has been suggested that all three muscarinic-receptor subtypes may play a role in asthma etiology (119). Neither atropine nor ipratropium bromide successfully differentiates between subtypes (120). Because of the possibility that indiscriminate blockade of muscarinic receptors may increase release of acetylcholine via a feedback mechanism, it seems possible that agents which selectively block the smooth muscle receptors (M₃) may have better profiles than present drugs (120). However, more than half the cholinergic receptors in human lung are of the M₁ subtype, so this view may represent an oversimplification (119).

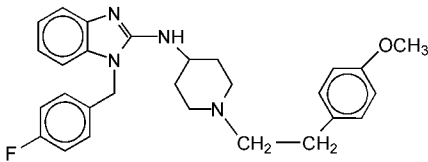
Agents Undergoing Clinical Evaluation

Antihistamines. Antihistamines are not recommended for the symptomatic treatment of asthma, although recent studies have shown that histamine (20) (Table 4) released from mast cells may account for 50% of the immediate asthmatic response (see HISTAMINE AND HISTAMINE ANTAGONISTS) (122). Reviews on antihistamines in asthma therapy may be found in references 124–127. The possible role of histamine in the anaphylactic response was first recognized in the early 1900s (123). Almost 40 years passed before compounds became available which were sufficiently nontoxic to be tried in clinical studies. These early agents, tested as therapeutic agents for allergic rhinitis and asthma (128), were only weakly active as antihistamines. They were not specific for histamine receptors and activity at muscarinic (cholinergic) and adrenergic receptors contributed both to bronchodilating actions and to a wide variety of side effects which limited use.

Table 4. Histamine and Antihistamines

Name	CAS Registry Number	Molecular formula	Structure number	Structure
histamine	[51-45-6]	C ₅ H ₉ N ₃	(20)	
clemastine	[15686-51-8]	C ₂₁ H ₂ ClNO	(21)	
chloro-pheniramine	[132-22-9]	C ₁ H ₁₉ N ₂ Cl	(22)	
terfenadine	[50679-08-8]	C ₂₀ H ₄₁ NO ₂	(23)	

astemizole [68844-77-9] C₂₈H₃₁N₄FO (24)



The discovery that histamine receptors, just like adrenergic and cholinergic receptors, may be divided into subtypes H₁ and H₂, combined with the recognition that the bronchial receptors were of the H₁ type, set the stage for a newer generation of antihistamines. Clinical investigation in the late 1970s of the H₁-antihistamines clemastine (21) (129) and chlorpheniramine (22) (130,131), shown in Table 4, revealed that these agents had a bronchodilating effect and provided some protection against exercise-induced asthma. But the side effects, induced at H₁-receptors in the central nervous system which produced sedation and at cholinergic receptors, limited the maximal doses that could be given. These drugs were not useful as antiasthmatic agents.

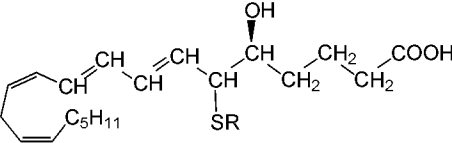
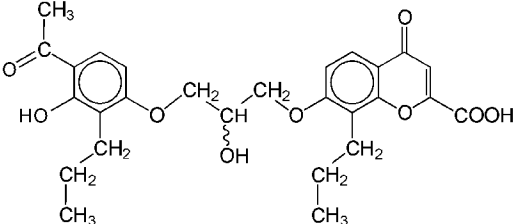
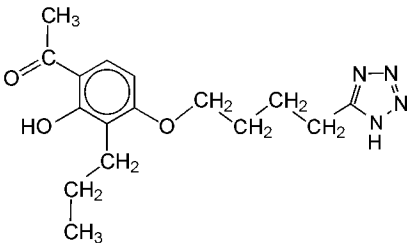
Two newer potent selective H₁-antagonists, terfenadine (23) (132) and astemizole (24) (133), have been developed which have neither the sedative nor the anticholinergic liabilities of the earlier agents. Both of these compounds have proven efficacious in the treatment of hay fever and produce very few side effects, prompting a re-evaluation of the role of antihistamines in asthma treatment.

Astemizole has very unusual pharmacokinetic parameters. It shows delayed onset both *in vitro* and *in vivo* (126) and also has a very long duration of action. *In vivo* formation of the desmethyl metabolite, equiactive to astemizole as an H₁-antagonist, occurs. This metabolite is cleared at only 1/10th the rate of astemizole. Clinically, it may take two days following a dose of astemizole for symptom alleviation to occur in the treatment of hay fever (134). However, the effect is very long lasting: after a single 10-mg tablet, significant antihistaminic activity can be demonstrated in volunteers for about 20 days (135). Astemizole seems to delay the onset of exercise-induced asthma but not affect the severity of the bronchoconstriction (136,137). Also, prolonged astemizole treatment offers some protection from the symptoms of seasonal asthma with significant attenuation of the early component of bronchoconstriction but little effect on the late-phase response (138).

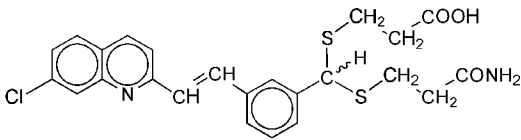
Oral terfenadine has a relatively rapid onset (134), and a sufficiently long duration of action that it needs to be dosed only once or twice a day. Clinical studies show: it effectively blocks histamine-induced bronchospasm (124); it causes modest bronchodilation (139,140); and it provides limited protection against either exercise-induced asthma (140,141) or challenge using nebulized water (139). The bronchodilatory response to 120-mg oral terfenadine has been shown to approach that of 200-μg of inhaled albuterol (4, R = C(CH₃)₂) (142). Terfenadine, however, has no effect on the dose of methacholine needed to cause a 20% fall in FEV₁ (143). Also, it has only a very modest protective effect against antigen-induced asthma, that effect being partial blockade of the immediate bronchoconstrictor response (144). Studies on its use in the treatment of seasonal atopic asthmatics have shown minor, but statistically significant, effects which have correlated with a reduction in the need to use other bronchodilators (125,145).

Leukotriene Antagonists. Over 50 years ago a second component, besides histamine, of the immediate type hypersensitivity reaction was identified (146). This discovery was named the slow reacting substance of anaphylaxis (SRS-A). Because it was believed that SRS-A played a primary role in the etiology of asthma and other diseases, the discovery generated a great deal of interest. However, determination of SRS-A structure and development of either antagonists or biosynthesis inhibitors was severely hampered by the limited availability of SRS-A from biological sources and chemical and biological instability (147). In 1980 it was shown that SRS-A was made up of a mixture of leukotrienes (148), which were products of the 5-lipoxygenase pathway of arachidonic acid metabolism (see PROSTAGLANDINS). Tests showed that the pure leukotrienes are 100 to 1000 times as potent as histamine in terms of bronchial spasmogens both *in vitro* and in clinical studies, prompting a resurgence of interest in the development of leukotriene antagonists and biosynthesis inhibitors. At this writing, only work in receptor antagonists has progressed far enough to show promise in the clinic. The leukotrienes are listed in Table 5 as are some antagonists.

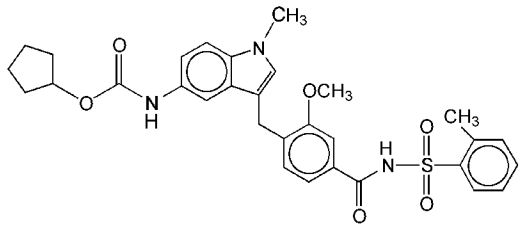
Table 5. Leukotrienes and Leukotriene Antagonists

Name	CAS Registry Number	Molecular formula	Structure number	Structure
<i>Leukotrienes</i>				
leukotriene	[72025-60-6]	C ₃₀ H ₄₇ N ₃ O ₉ SC ₂	(25, RSH = glutathione)(25,	
C ₄ leukotriene	[73836-78-9]	C ₅ H ₄₀ N ₂ O SC ₂ H	RSH = cysteinylglycine)(25,	
D ₄ leukotriene E ₄	[75715-89-8]	C ₃₇ H ₅₁ NO ₅ S	RSH = cysteine)	
<i>Leukotriene antagonists</i>				
FPL-55712	[40786-08-1]	C ₂₇ H ₃₀ O ₉	(26)	
LY-171883	[88107-10-2]	C ₃₁ H ₂₂ N ₄ O ₃	(27)	
MK-571 (formerly	[115104-28-4]	C ₂₄ H ₂₃ N ₂ O ₃ ClS ₂	(28)	

L-660711)



ICI-204219 [107753-78-6] C₃₁H₃₃N₅O S (29)



The first SRS-A antagonist, FPL-55712 (26) (149), was discovered before the structures of the leukotrienes were determined. Although this compound is relatively weak as an antagonist and suffers from a very short half-life *in vivo*, it played an important role both in leukotriene structure elucidation and as a model for later antagonists. In work structurally related to FPL-55712, LY-171883 was developed (27) (150). LY-171883 was evaluated in several clinical trials before development was stopped. Orally administered, LY-171883 blocked slightly the response to aerosol LTD₄, improved pulmonary function (FEV₁) in mild asthmatics (151), decreased the sensitivity of asthmatics to cold air-induced bronchoconstriction (152), and significantly reduced the bronchoconstrictor response to inhaled antigen (153). However, in all these studies the beneficial effects were minimal.

Many structurally diverse newer leukotriene antagonists that are at varying stages of development have since been discovered (154,155). Two compounds which are especially potent and which seemed most promising as potential antiasthmatic agents are MK-571 (formerly L-660711) (28) (156), and ICI-204219 (29) (157). Both of these agents advanced to the clinic but the development of MK-571 has since been discontinued. However, studies show that two hours after a single 40-mg po dose, ICI-204219 caused a greater than 100-fold shift in the dose-response curve to aerosol LTD₄ (158), and caused a greater than tenfold shift in the dose-response to inhaled antigen (159).

Other Drugs. In addition to the drugs already discussed, a wide variety of other agents have been investigated for antiasthmatic potential. For example, a large but unsuccessful effort went into the search for a prostaglandin-type bronchodilator in the 1970s. Within this general area the uncertain role of thromboxane as a mediator in asthma has prompted limited interest in the exploration of thromboxane A₂ synthesis inhibitors and or antagonists (160,161).

In 1990 5-lipoxygenase inhibitors, ie, leukotriene biosynthesis inhibitors, began undergoing clinical evaluation (161,162). Also, rapidly approaching clinical evaluation are a structurally diverse group of platelet-activating factor (PAF) antagonists (162). In humans, PAF is a potent bronchospastic agent that also induces bronchial hyperreactivity. There is significant effort being expended to discover and develop potent PAF antagonists as antiasthmatic agents (163,164).

The key to a cure for asthma is presumably to be found in a better understanding of its etiology. Until then, there are many approaches being utilized (165). As an example, there is interest in discovering a drug which would specifically affect calcium ions in airway smooth muscle and cause bronchodilation. Similarly, if selective potassium channel openers can be found, they should act as bronchodilators. Alternatively, a selective inhibitor of the correct phosphodiesterase isozyme should mimic the bronchodilating effects of the β₂-agonists without inducing the side effects. Formation of both the prostanoid and leukotriene bronchoconstrictors as well as platelet activating factor should theoretically be inhibited, if a selective phospholipase A₂ inhibitor can be discovered. Finally, the roles of the nonadrenergic, noncholinergic nervous system (38) and the neuropeptides, eg, tachykinins, in asthma have only begun to be explored.

Economic Aspects

Total sales of prescription bronchodilators and antiasthma products in 1989 were approximately \$1.2 and \$3.3 billion in the North American and world markets, respectively (166). The three largest shares of the world market were held by: Glaxo Holdings plc, Schering-Plough Corporation, and Boehringer Ingelheim Corporation.

In 1989 β₂-agonists were the largest class of prescription bronchodilators and antiasthma agents. Total sales reached approximately \$1.2 billion. Albuterol (4, R = C(CH₃)₃) was the best-selling (ranked by dollar value) antiasthmatic agent (167). Most of the remaining β₂-agonist sales were for terbutaline (3, R = C(CH₃)₃) and metaproterenol (3, R = CH(CH₃)₂). Inhaled corticoids were the next largest class. Corticoid sales, which reached approximately \$400 million, were predominantly accounted for by beclomethasone dipropionate (14) and budesonide (15). Sales of nonprescription, over-the-counter, antiasthma products are only a small fraction of the prescription market.

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ANTIATHEROSCLEROTIC AGENTS.

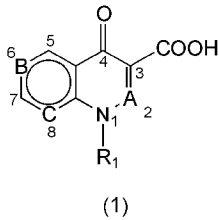
See [CARDIOVASCULAR AGENTS](#).

ANTIBACTERIAL AGENTS, SYNTHETIC

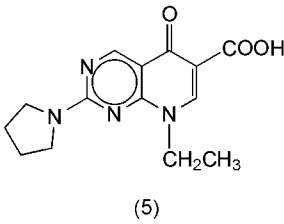
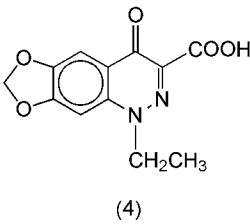
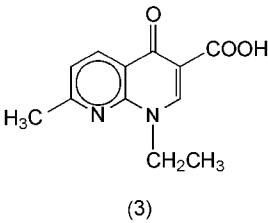
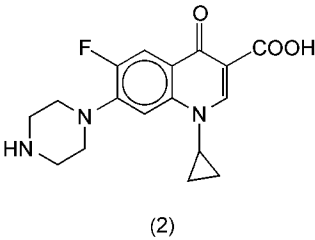
Quinolones,
Nitrofurans,
Sulfonamides,

QUINOLONES

Quinolone carboxylic acids are a class of totally synthetic antibacterial agents which have the general structure (1).



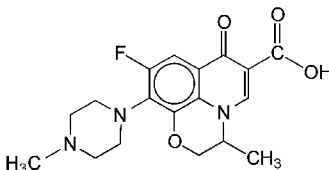
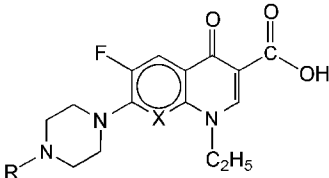
This representation is intended to encompass 4-oxo-3-quinolinecarboxylic acids as well as the corresponding 1,8-naphthyridines, cinnolines, and pyrido[2,3-*d*]pyrimidines. These classes are illustrated by ciprofloxacin [85721-33-1] (2) (1), nalidixic acid [389-08-2] (3) (2), cinoxacin [28657-80-9] (4) (3), and piromidic acid [19562-30-2] (5) (4), respectively.



Nalidixic acid was the first quinolone introduced to clinical practice, and it is still in use today for the treatment of urinary tract infections caused by gram-negative pathogens (5,6). Since the introduction of nalidixic acid in the early 1960s, substantial improvements have been made in the antibacterial spectrum and potency of quinolones. Additionally, newer quinolones are well absorbed and distributed throughout the body making them useful for the treatment of a variety of systemic infections including those of the respiratory tract, gastrointestinal tract, the ear, nose, and throat, sexually transmitted diseases, and bone infections (7–9). Because of rapid advances in the development of quinolone antibacterial agents since the 1980s, they are now important tools available to physicians. Established quinolone antibacterial agents are presented in Table 1.

Table 1. Commercially Significant Quinolone Antibacterial Agents

Quinolonecarboxylic acid ^a	CASRegistry Number	Structure	Company	Indications
ciprofloxacin (2)	[85721-33-1]	^b	Bayer	lower RTI ^c , skin and soft tissue, bone and joint, UTI ^d , and infectious diarrhea
ofloxacin (6a)	[83380-47-6]		Daich Seiyku	UTI, GUT ^e , GI tract, RTI, skin and

			soft tissue	
enoxacin (7)	[74011-58-8]	Dainippon	UTI, GUT, skin infections, upper and lower RTI, and GI tract infection	
				
		where R = H, X = N		
norfloxacin (8)	[70458-96-7]	7, where R = H, X = CH	Kyorin	UTI
pefloxacin (9)	[70458-92-3]	7, where R = CH ₃ , X = CH	Roger Bellon (Rhône-Poulenc)	UTI, RTI, bone and joint infections, meningitis, septicemia, and endocarditis

^a The systematic names are as follows: (2) 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; (7) 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid; (8) 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; (6a) 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-*de*] [1,4]benzoxazine-6-carboxylic acid; (9) 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

- ^b In text.
^c Respiratory tract infection.
^d Urinary tract infection.
^e Genito-urinary tract infection.

Structure–Activity Relationships

The most important structural features necessary for meaningful antibacterial activity of quinolones include a carboxylic acid attached to the 3-position of the quinolone nucleus and a small alkyl or aryl group in the 1-position. In addition to these more or less rudimentary requirements for activity (10), all of the newer generation quinolones have a fluorine attached to the 6-position and a nitrogen heterocycle attached to the 7-position. This heterocycle is often a piperazine or pyrrolidine derivative. Comparison of the data in Table 2 for nalidixic acid (3) and cinoxacin (4), nonfluorinated quinolones that lack a nitrogen heterocycle at position 7, with that for norfloxacin (8) (11), enoxacin (7) (9), and pefloxacin (9) (12) underscore the advantage of these modifications in newer generation quinolones. Nalidixic acid and cinoxacin have modest activity against *E. Coli* whereas the three later compounds are much more active against a wider spectrum of bacteria.

Table 2. Antibacterial Activity of Representative Quinolones^a

Quinolone	Minimum Inhibitory Concentration, µg mL						Refs.
	EC	PA	BF	SA	SF	SP	
(3)	2–8	64–256	32	32	>32	128–256	3,13
(4)	2–4	>256	>32	>32	32	>256	3,13
(8)	0.03–1	0.25–4	16–128	0.5–8	2–8	2–8	14–16
(17)	0.06–0.5	0.5–8	8	1	8	1	13,17
(7)	<0.12	2	4	0.5	2	2	13
(9)	0.06–2	0.05–4	8–16	0.25	4	2	13,16
(19)	0.004–0.5	0.5–2	1–4	0.06–0.25	1	0.25–1	13,18
(18)	0.008–0.25	0.03–2	0.5–2	0.008–0.5	0.25	0.06	13,19
(2)	0.008–0.25	0.06–0.5	4–32	0.25–2	0.5–2	0.25–2	14–16
(6a)	0.03–0.25	0.5–8	2–16	0.25–1	2–4	0.5–4	14,16,17
(13)	0.004	2	0.12	0.015	0.03	0.015	13
(16)	0.03–1	1–32	0.06–5	0.008	0.06	0.008–0.03	13,14,17

^a These determinations were performed at Sterling Drug, Inc. The organisms used for the measurements were *E. Coli* ATCC 1-25922 (EC), *P. Aeruginosa* ATCC 27853 (PA), *B. Fragilis* ATCC 25285 (BF), *S. Aureus* ATCC 29213 (SA), *S. Faecalis* ATCC 29212 (SF), and *S. Pyogenes* ATCC 6301 (SP). Other values are taken from the literature for a large number of organisms of each strain.

The 6-fluorine provides a significant enhancement in antibacterial activity for many quinolones presumably by increasing cellular penetration (11,20) and the inhibitory activity against the enzyme. In the case of norfloxacin, a fluorine at the 6-position provides a compound which is 16-fold more potent against *E. Coli* than the nonfluorinated derivative (21–24). Substituents other than fluorine at the 6-position have provided some enhancement in activity over the 6-H compound, but this has been less than that provided by fluorine (11). In some cases the effect of the 6-fluorine is much smaller, depending on the group at the 7-position (25,26).

In earlier quinolones a number of groups were placed at the 7-position of the quinolone nucleus, including heterocycles attached to this position as well as a number of 6,7- and 7,8-ring fused derivatives. Many of these earlier variations have been extensively reviewed (10). In newer clinically important quinolones, the 7-position usually contains a piperazine derivative (see Fig. 1 and Table 3). Piperazine mimics for quinolones have been introduced in the form of 3-(aminomethyl)pyrrolidines (27). Pyrrolidinyl quinolones of this type, represented by CI-934 [91188-00-0] (12) (28), PD-117,558 [99734-97-1] (13) (29), and DS-4524 (10) (30) offer improvements over their piperazinyl counterparts in the form of increased gram-positive activity. When the 7-piperazine is replaced by an azole substituent (31), the resulting antibacterial activity is similar to that of the piperazinyl relatives. Idoxacin (15), an example of the azole replacement for the piperazine, may offer some advantages over the piperazinyl with respect to gram-positive activity, particularly *Staphylococcus* strains (32). Win 57,273 [123942-02-1] (16), a quinolone with a 2,6-dimethyl-4-pyridinyl group at the 7-position, shows good gram-positive activity particularly against *S.*

Aureus and additionally, this agent exhibits excellent potency against anaerobes (14,17). Good activity against anaerobic organisms is still uncommon for quinolones (33).

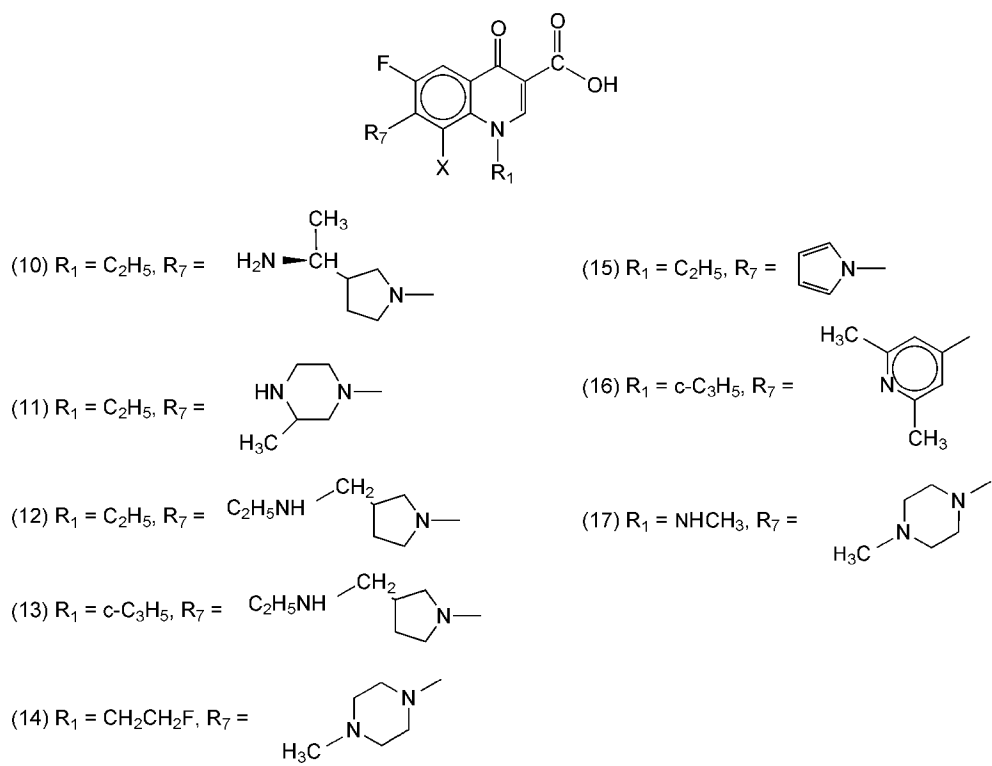


Fig. 1. Piperazine and pyrrolidine substitution at the 7-position of quinolones. For (10)–(14) X = F, in (15)–(17), X = H.

Table 3. Quinolones in Development

Quinolonecarboxylic acid ^a	CAS RegistryNumber	Structure	Company
DS-4524 (10)	[107333-96-0]		Daiichi
lomefloxacin (11)	[98079-51-7]		Hokuriku Seiyaku
fleroxacin (14)	[79660-72-3]		Monsanto
tosufloxacin (18) ^c	[100490-36-6]		Kyorin Roche
			Toyama Abbott
sparfloxacin (21)	[110871-86-8]		Dianippon Warner-Lambert
DR-3355 (6b)	[10986-85-4]		Daiichi Seiyaku
rufloxacin (20)	[101363-10-4]		Mediolanum
temafloxacin (19)	[105784-61-0]		Abbott Tanabe Seiyaku
amifloxacin (17)	[86393-37-5]		Eastman Kodak Yamanouchi
idloxacin (15)	[91524-15-1]		Esteve

^a The systematic names are as follows: (10) (R*, S*)-7-(3-(1-aminoethyl)-1-pyrrolidinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

(**11**) 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; (**14**) 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; (**18**) D,L-7-(3-amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid; (**21**) 5-amino-1-cyclopropyl-6,8-difluoro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4(1*H*)-oxo-3-quinolinecarboxylic acid; (**6b**) (*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid; (**20**) 9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid; (**19**) 1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; (**17**) 6-fluoro-1,4-dihydro-1-(methylamino)-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; (**15**) 6-fluoro-7-(pyrrol-1-yl)-1-ethyl-1,4-dihydro-4-oxo-3-quinoline carboxylic acid.

^b See Figure 1.

^c This agent was launched in Japan during April, 1990.

^d In text.

^e See Table 1; (**6a**) represents the racemate. (**6b**) is the (*S*)-enantiomer.

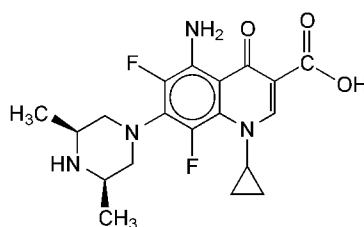
An ethyl group at the 1-position was found to be optimum in earlier quinolones when compared with a methyl or propyl group at this position, and thus, based on these steric considerations, retained in many subsequent quinolone structures. Other groups at the 1-position include the 2-fluoroethyl substituent in fleroxacin (**14**) (23,34,35), and an aminomethyl group in amifloxacin (**17**) (36,37); these groups all have similar steric requirements. Along with norfloxacin, these agents offer good gram-negative activity, particularly against *E. Coli*.

Steric factors, however, are not the only important considerations for groups at the 1-position. Ciprofloxacin (**2**) (**1**) with a cyclopropyl group in the 1-position, when compared with its ethyl analogue norfloxacin in Table 2, offers increased antibacterial potency by 4–8 times against many organisms and approximately 30-fold against *E. Coli*. Additionally, ciprofloxacin has improved *in vivo* potency over norfloxacin (38). The increase in activity afforded by the cyclopropyl substituent over that of the ethyl cannot be explained simply on steric grounds and it was suggested that through space, electronic interactions may be important (39). The 2,4-difluorophenyl group in tosufloxacin (**18**) (**18**) and temafloxacin (**19**) (**19**) provides these agents with excellent antibacterial activity comparable with that found for ciprofloxacin, and also gives these agents *in vivo* activity superior to that offered by ciprofloxacin. Quinolones with a *tert*-butyl group at the 1-position also compare favorably with ciprofloxacin (**40**).

Another important development in the structure–activity relationships of quinolone antibacterials came with the introduction of the 1,8-bridged quinolone ofloxacin (**6a**). In this quinolone, the movement of the ethyl group at the 1-position is restricted by "tying" it to the 8-position in the form of a 1,4-benzoxazine ring. *In vitro* activity improvements are found that are more or less comparable to the improvements noted with ciprofloxacin (35,41–43). A variation on ofloxacin is rufloxacin (**20**); this compound lacks the methyl group on the 1,8-bridge and contains a sulfur in place of the oxygen attached to the 8-position. Rufloxacin, although less potent than ofloxacin, is well absorbed and has longer half life than does ofloxacin (44–46).

When ofloxacin was first introduced it was made available as the racemate. Later the optical isomers were prepared and it was found that the (*S*)-enantiomer, DR 3355 (**6b**), was substantially more active (8–128-fold) than the (*R*)-isomer against a broad range of bacteria (47–50). This chiral preference is not unique to ofloxacin and has been demonstrated in other quinolones as well (51,52). This significant finding has already had an impact on the design of new quinolone antibacterials still in development (53).

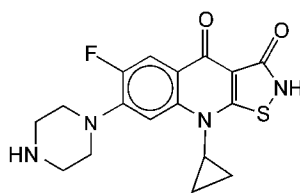
The 5-position of quinolones can be substituted by small groups such as halogens, hydroxyl, or amino (54–56). The amino group at this position can be advantageous, particularly when applied to 6,8-difluoro-7-piperazinyl or 6,8-difluoro-7-pyrrolidinyl quinolones. In contrast to 6,8-difluoro quinolones, when this replacement is applied to ofloxacin, the resulting derivative has reduced antibacterial activity (57). Replacement of the 5-amino group with methylamine or dimethylamine causes activity to drop substantially. Sparfloxacin [110871-86-8] (**21**), a representative of 5-amino-6,8-difluoro quinolones, affords modest improvements in gram-positive activity as well as increased *in vivo* potency when compared with both ciprofloxacin and ofloxacin (54).



(**21**)

The 8-position of the quinolone nucleus can often be advantageously substituted by fluorine (58) or chlorine (59) to give compounds with improved antibacterial potency over hydrogen in this position. With 1,8-naphthyridines, activity is reported to be approximately equivalent to the quinolone bearing a hydrogen in this position (60). As an example of this, see the data for norfloxacin (**8**) and enoxacin (**7**) in Table 2.

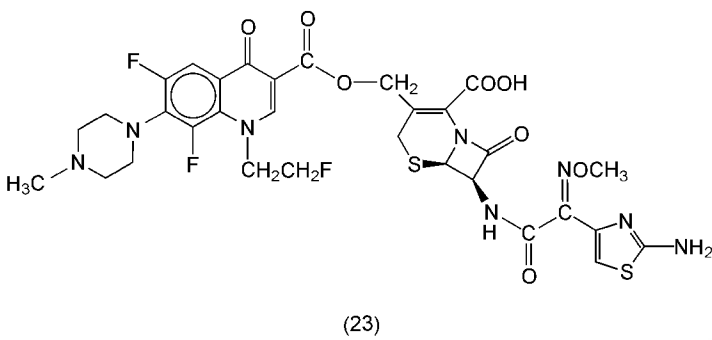
A surprising development involving the 3-position has been presented (61,62). This position traditionally has had a carboxylic acid group and attempts to replace the carboxylate have resulted in lower antibacterial activity. However, it was demonstrated that the carboxylate could be replaced with an isothiazolo ring fused between the 2- and 3-position of the quinolone nucleus. A-62824 [111279-87-9] (**22**), illustrates this structural modification as applied to ciprofloxacin.



(**22**)

This replacement results in compounds which are several times more active than their 3-carboxylate counterparts and they show this activity against a broad range of bacteria as well as against the target enzyme. No *in vivo* antibacterial activity has been described.

Quinolone-Cephalosporin Codrugs. Quinolones have been covalently linked to cephalosporins in order to generate a codrug containing one molecule of each type of antibacterial agent. An example is the fleroxacin-cefotaxime [63527-52-6] combination, Ro 23-9424 [115622-58-7] (**23**).



In essence, the cephalosporin acts as a carrier (63) for the quinolone. The quinolone is replaced in the bacterial cell after the action of β -lactamase on the cephalosporin portion of the molecule. This codrug combination represents a relatively new class of antibacterial agents which appear to offer advantages over the separated components (64). A good introductory discussion of these exciting agents can be found (65) (see also ANTIBIOTICS; β -LACTAMS; CEPHALOSPORINS).

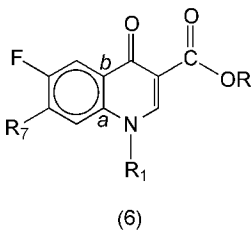
Mechanism of Action

Quinolones exert their antibacterial activity by interfering with the replication of bacterial DNA (66,67) by inhibition of the enzyme DNA gyrase through the formation of a quinolone-DNA-enzyme complex (68–70). The critical reaction, catalyzed by the enzyme, is the negative supercoiling of bacterial DNA, a process involving the breaking and resealing of double-stranded circular DNA.

This enzyme has been shown to have two subunits referred to as A and B (71). The B subunit is responsible for supplying the energy needed for the supercoiling reaction (72); this process is inhibited by a class of antibiotics called coumermycins. The coumermycins competitively bind to the B subunit thereby blocking the binding of ATP. Quinolones do not interact with the B subunit, but exert their effect on the processes of the A subunit. One model proposed that quinolones, unlike coumermycins, do not bind to the enzyme, but have DNA as their molecular target (73). This model was later refined indicating that a gyrase-DNA complex is inhibited by quinolones (74). The essence of this refined model (74,75) is that gyrase interacts with DNA causing the double-strand break needed for strand passage in the supercoiling process. Once the DNA strands are cut, the protruding ends provide a site to which quinolones can bind. When this occurs, the supercoiling process is stopped and, along with it, gyrase turnover.

Preparation of Quinolones

The general method by which most newer fluoro quinolones are prepared involves a ring closure reaction to form the quinolone nucleus by forming one of the highlighted bonds, *a* or *b*, shown in general structure (24).



In the general preparation of quinolones by forming the nitrogen aryl bond *a* in the ring closure, typical precursors are prepared as shown in Figure 2. The ring closure involves nucleophilic displacement of a halogen, usually a chlorine or fluorine (76); eg, (29) and (30) lead to (31) [86483-54-7] and (32) [123942-15-4], respectively.

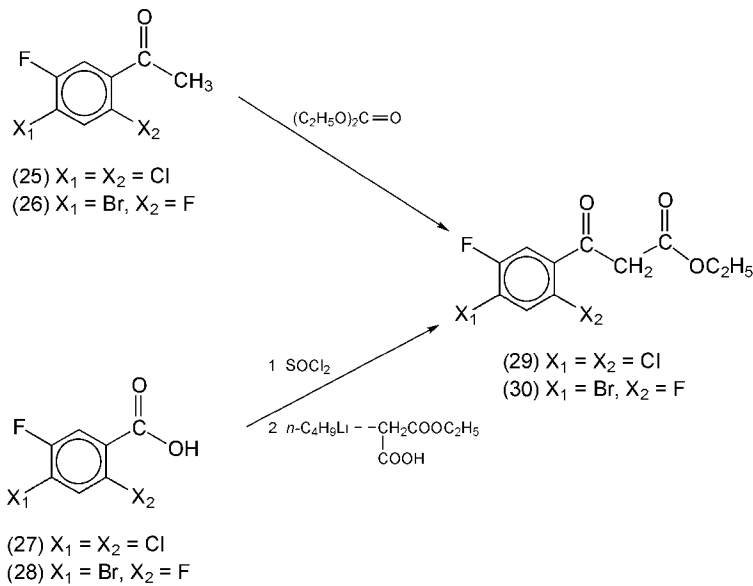
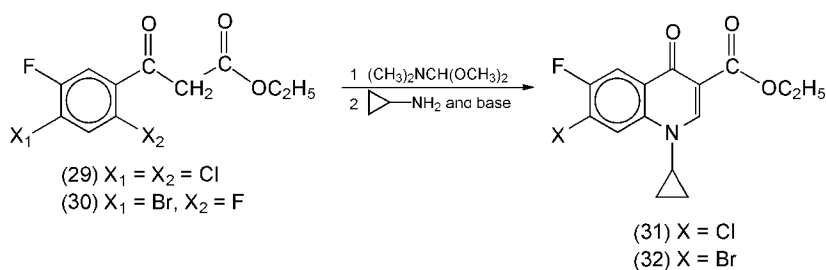
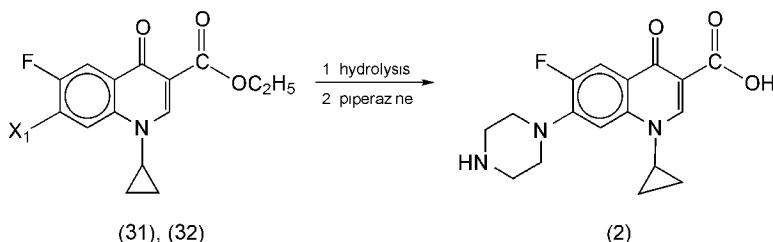


Fig. 2. Preparation of precursors for closure to structure (24) at the *a* bond. (25) 2,4-dichloro-5-fluoroacetophenone [704-10-9]; (26) 4-bromo-2,5-difluoroacetophenone [123942-11-0]; (27) 2,4-dichloro-5-fluorobenzoic acid [86522-89-6]; (28) 4-bromo-2,5-difluorobenzoic acid [28314-82-1]; (29) ethyl 3-(2,4-dichloro-5-fluorophenyl)-3-oxopropanoate [86483-51-4]; (30) ethyl 3-(2,5-difluoro-4-bromophenyl)-3-oxopropanoate [123942-12-1].

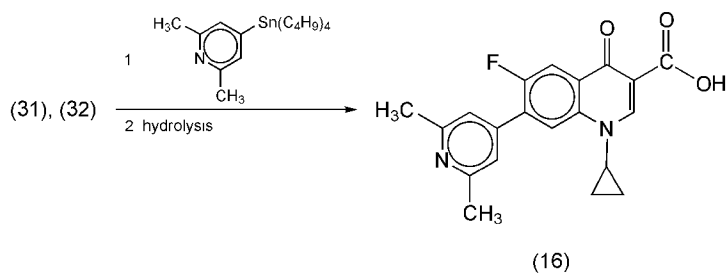


Alternatively, $\text{HC}(\text{OC}_2\text{H}_5)_3$ may be used in step 1. The appropriate R_7 group is attached by a second nucleophilic displacement to give the desired quinolone.



This is a general reaction as the heterocyclic group of most newer quinolones is derived from a nucleophilic piperazine or pyrrolidine derivative (11,47,53,54).

In the synthesis of Win 57,273 the attachment of the R_7 group, a 2,6-dimethylpyridinyl group, involves formation of a carbon-carbon bond rather than a carbon-nitrogen bond. The method for the attachment of this group is a palladium mediated coupling reaction (77,78) of 4-tributylstannyl-2,6-dimethylpyridine [122033-61-8] with a 7-haloquinolone (26).



This coupling works best when the halogen at the 7-position is bromine rather than chlorine or fluorine. This represents the first application of this coupling reaction to the intact quinoline nucleus and thus represents an important advance in quinolone chemistry.

The alternative cyclization route is one which forms bond *b* in the ring closure reaction. This process is illustrated for norfloxacin (11) in Figure 3. In this sequence, 3-chloro-4-fluoro-aniline [367-21-5] and diethyl ethoxymethylenemalonate [87-13-8] are heated to displace ethanol giving the intermediate propanedioate [70032-30-3]. Thermal cyclization is achieved in diphenyl ether [101-84-8] to form the quinolone nucleus in (33) [75073-15-3]. Subsequent alkylation and hydrolysis gives (34) [70458-94-5]; displacement of the 7-chlorine by piperazine [110-85-0] gives norfloxacin (8). The Gould-Jacobs method described (79) is limited to quinolone targets in which the group on the 1-position is derived from a reasonably reactive alkyl halide.

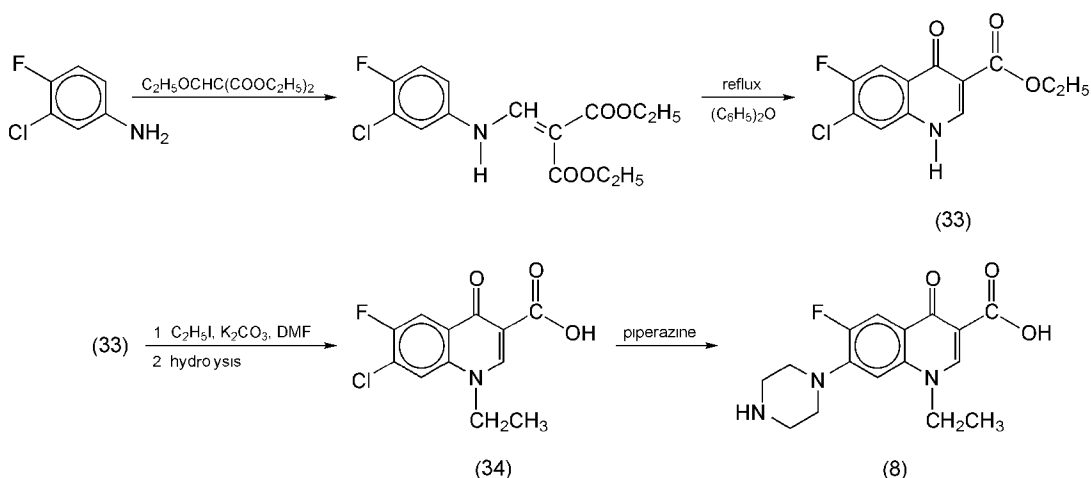


Fig. 3. Cyclization to form ring bond *b* in (24).

Safety of Quinolone Antibacterial Agents

For the most part quinolones are well tolerated with few reports of adverse reactions (80,81), but there are some concerns, one of which is that they cause arthropathy in juvenile animals. This is a condition in which the cartilage of weight-bearing joints is damaged. Because of this concern, quinolones are contraindicated for children and during pregnancy. A second problem is that of adverse side effects including those of the central nervous system (CNS) and also adverse reactions when quinolones are taken with other drugs (82). The CNS side effects may, in part, be related to the affinity of quinolones to γ -aminobutyric acid receptors thus inhibiting the binding of this important neurotransmitter (83). When quinolones are taken along with other drugs, adverse side reactions can stem from a variety of causes. In the case of theophylline [5967-84-0], an antiasthmatic, the side effects may be related to the inhibition of the metabolism of this drug (84,85). Adverse reactions should decrease with more recent quinolones such as lomefloxacin, sparfloxacin, and temafloxacin (86–90). A useful discussion of quinolone toxicity and safety has appeared (91).

Resistance. Resistance to quinolones, particularly to newer agents (6), is not a significant problem at this time (92). The resistance that has been

found is the result of mutation of the gene for the A subunit of the gyrase enzyme. A second mode of resistance results in decreased drug permeation resulting from a change in the outer membrane protein of the bacterial cell (93).

Economic Aspects

The domestic antiinfective market is in excess of \$3 billion and the global market surpasses \$8 billion (94,95). Earlier quinolones have had little impact on this market as their utility was limited primarily to urinary tract infections. Sales of cinoxacin, for example, are on the order of \$4 million. Newer quinolones, because of their safety, seemingly low propensity toward bacterial resistance, and vastly improved therapeutic utility, now enjoy a much greater share of this market. This is especially true for ciprofloxacin, the most important quinolone antibacterial agent. Sales of ciprofloxacin exceeded \$135 million in the United States in 1988, \$260 million in 1989, and were reported at \$385 million in 1991. Additionally, ciprofloxacin will soon be available as an intravenous formulation allowing it to be used to treat a greater number of patients and thus assuming a larger portion of this market (96–98). The wholesale price of ciprofloxacin (99) for 50 tablets is \$84.03, \$90.04, and \$174.07 for 250 mg, 500 mg, and 750 mg sizes, respectively. This translates to a cost of \$3.36 per day for twice a day dosing. Although these costs are higher than other antibacterial agents, overall savings should be realized (95) compared to other types of therapy necessitated by nonorally active agents, including hospitalization (81).

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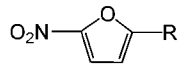
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NITROFURANS

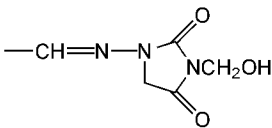
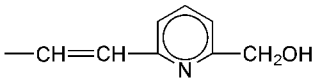
The nitrofurans encompass a class of synthetic antibacterials characterized by the 5-nitro-2-furanyl group:



With relatively few exceptions, the R function contains the azomethine (—CH=N—) moiety. The most prominent exceptions contain the olefinic (—C=C—) moiety (Table 1).

Table 1. Structures of Representative Antibacterial Nitrofurans

Name	CAS Registry Number	Molecular formula	
furium	[531-82-8]	C ₉ H ₇ N ₃ O ₄ S	
furazolidone	[67-45-8]	C ₈ H ₇ N ₃ O ₅	
Z-furan furylfuramide	[710-25-8] [3688-53-7]	C ₇ H ₇ N ₂ O ₄ C ₁₁ H ₈ N ₂ O ₅	—CH=CH—CONH₂
nitrovin	[2315-20-0]	C ₁₄ H ₁₂ N ₂ O ₅ · HCl	
furalazine ^a	[566-12-7]	C ₉ H ₇ N ₅ O ₃	
acetylfuratrizine ^b	[1789-26-0]	C ₁₁ H ₉ N ₅ O ₄	
panfuran-S ^c	[794-93-4]	C ₁₁ H ₁₁ N ₅ O ₅	
nifuroxime	[6236-05-1]	C ₅ H ₄ N ₂ O ₄	—CH=NOH (anti)
nitrofurazone	[59-87-0]	C ₇ H ₄ N ₄ O ₄	—CH=N—NHCONH ₂
nifuraldezone	[3270-71-1]	C ₇ H ₄ N ₄ O ₅	—CH=N—NHCOCONH ₂
nihydrazone	[67-28-7]	C ₇ H ₇ N ₃ O ₄	—CH=N—NHCOCH ₃
nitrofurantoin	[67-20-9]	C ₈ H ₇ N ₄ O ₅	
nifuratel	[4936-47-4]	C ₁₀ H ₁₁ N ₃ O ₅ S	
nitrofurathiazide	[61143-06-4]	C ₁₃ H ₁₂ N ₄ O ₅ S	

nifurtoinol	[1088-92-2]	C ₉ H ₈ N ₄ O	
nifurprinol	[13411-16-0]	C ₁₂ H ₁₀ N ₂ O ₄	

^a R' = R'' = H.

^b R' = H; R'' = CH₃CO

^c R' = R'' = —CH₂OH .

The antimicrobial activity of this class of compounds was first reported in 1943 (1) and this finding was described independently four years later (2). After investigation of several derivatives, it was concluded that the 5-nitro function was responsible for the observed antimicrobial activity (3). These preliminary findings focused attention on this area of research and as a result, several thousand nitrofurans have been prepared, and thousands of articles have been prepared, and thousands of articles have been published describing the extensive efforts in these areas.

Several nitrofurans have been marketed either regionally or worldwide in the human and veterinary areas because of their broad spectrum of activity, relatively mild toxicity, and low tendency for resistance development. However, accurate total volumes or sales of these products on a global basis are not generally available. In the United States, nearly four million prescriptions were written in 1989 for products containing nitrofurazone or nitrofurantoin. U.S. sales during this period for these products approached \$70 million; thus therapy with this class of compounds remains a significant therapeutic alternative.

Chemical Properties

Nitrofurans are generally stable, water-insoluble, crystalline solids, which decompose (darken) upon prolonged exposure to light or alkali. Their strong ultraviolet absorption provides the basis for analytical procedures for these materials. Chemical reduction of these nitro compounds gives rise to amino derivatives (4) as well as products of ring-opening (5,6). Nucleophiles which have been shown to displace the nitro function include methoxy (7,8), halogen (9), azido (10), alkylmercapto (10), and phenylsulfonyl (10). Photochemical hydroxylation of 5-nitro-2-furancarboxaldehyde gives rise to the 4-hydroxy derivative (11).

Biological Mechanism of Action

The mechanism of action of selected members of this class has been investigated. Nitrofurantoin is bactericidal at the concentrations achieved in the urinary tract and highly effective against the corresponding pathogens (12). Since its introduction for use in uncomplicated urinary tract infections, essentially no resistance development has occurred, unlike nearly all other antimicrobials. This is believed to be because of the ability of the nitrofurans to affect multiple cytoplasmic targets such as citric acid cycloenzyme, bacterial DNA and RNA, and ribosomes essential for bacterial function. Both nitrofurazone (13) and nitrofurantoin (12) are metabolized to reactive intermediates that facilitate inhibitory processes at multiple sites such that a low probability of simultaneous resistance development exists. Potential intermediates have been postulated to be hydroxylamines, nitrosamines, and free radicals.

Mutagenic and Carcinogenic Activity

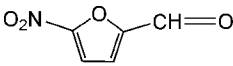
Although *in vitro* mutagenicity tests suggest that some nitrofurans in general provoke a positive response, use of *in vivo* mammalian systems has produced equivocal or negative results.

It is not appropriate to generalize the carcinogenicity of this class of compounds. Nitrofurazone appears to increase the incidence of benign mammary tumors in rats. The tumorigenic activity of furazolidone is expressed by an increase in the incidence of spontaneous tumors in both mice and rats. Bioassays of nitrofurantoin in several species of mice and rats failed to reveal any evidence of direct tumorigenic activity. Ovarian tumors have been reported in B C₃F₁ mice, but these are believed due to an indirect expression of toxicity (14,15).

These three nitrofurans have been used therapeutically for over 30 years with no reports of human neoplasia and the relevance of the animal findings to short term therapy in humans has not been established.

Preparation

Most commercialized nitrofurans are derived from 5-nitro-2-furancarboxaldehyde [698-63-5] or the corresponding diacetate.



These precursors are prepared by reaction of fuming nitric acid in excess acetic anhydride at low temperatures with 2-furancarboxaldehyde [98-01-1] (furfural) or its diacetate (16) followed by treatment of an intermediate 2-acetoxy-2,5-dihydrofuran [63848-92-0] with pyridine (17). This process has been improved by the use of concentrated nitric acid (18,19), as well as catalytic amounts of phosphorus pentoxide, trichloride, and oxychloride (20), and sulfuric acid (21). Orthophosphoric acid, *p*-toluenesulfonic acid, arsenic acid, boric acid, and stibonic acid, among others are useful additives for the nitration of furfural with acetyl nitrate. Hydrolysis of 5-nitro-2-furancarboxyaldehyde diacetate [92-55-7] with aqueous mineral acids provides the aldehyde which is suitable for use without additional purification.

An alternative route to 5-nitro-2-furancarboxaldehyde requires nitration of 2-furancarboxaldehyde oxime [1121-47-7] with mixed acid to give the nitrated oxime [555-15-7], and concomitant hydrolysis (22). Furthermore, 2-furan-carboxaldehyde derivatives with the R-substituent in place have been nitrated to the desired product (23).

Furium. N[4-(5-Nitro-2-furanyl)-2-thiazolyl]acetamide, has demonstrated activity against bacilli and pathogenic enterobacteria (24). The product, prepared from thiourea and 2-bromo-1-(5-nitro-2-furanyl)ethanone followed by acetylation of the intermediate aminothiazole with acetic anhydride in pyridine (25), is marketed in several countries for both human and veterinary use.

Furazolidone. 3-[(5-Nitro-2-furanyl)methyleneamino]-2-oxazolidinone, is manufactured by the condensation of 5-nitro-2-furancarboxaldehyde with 3-amino-2-oxazolidinone (19,26). The product is employed clinically for gastrointestinal and vaginal infections as well as an antibacterial and antiprotozoal agent in poultry and swine. Furazolidone has been shown to be metabolized to its 4-hydroxyfuryl derivative in rats (27) and to 3-(4-cyano-2-oxobutylideneamino)-2-oxazolidinone in several species (28).

Z-Furan. 3-(5-Nitro-2-furanyl)-2-propenamide, is prepared by condensation of 5-nitro-2-furancarboxaldehyde diacetate with malonic ester followed by PCl₅ chlorination and amination (29). The product was marketed in Japan as a food preservative.

Furylfuramide. α [(5-Nitro-2-furanyl)-2-methylene]-2-furanacetamide, withdrawn from the market in Japan in 1974 because of mutagenicity, is prepared by condensation of 5-nitro-2-furancarboxaldehyde with 2-furanacetic acid followed by chlorination and amination (30). The isomerization of *cis* to *trans* form of furylfuramide has been shown to occur in the presence of a variety of biological reducing agents (31).

Nitrovin. 2-{3-(5-Nitro-2-furanyl)-1-[2-(5-nitro-2-furanyl)ethenyl]-2-propenyldiene} hydrazinecarboximidamide hydrochloride has been marketed for both human and veterinary use as an antibacterial agent. The product, which has also seen use as a veterinary food additive (32), is prepared from 5-nitro-2-furan-carboxaldehyde and acetone followed by treatment of the resulting dione with aminoguanidine (33).

Furalazine, Acetylfuratrizine, Panfuran-S. Heating nitrovin in butanol or dimethylformamide at 100–130°C affords furalazine, 6-[2-(5-nitro-2-furanyl)ethenyl]-1,2,4-triazine-3-amine (34). An improved synthesis originates with 5-nitro-2-furancarboxaldehyde and acetone, proceeds through 4-(5-nitro-2-furanyl)-3-buten-2-one followed by a selenium dioxide oxidation to the pyruvaldehyde hydrate, and subsequent reaction with aminoguanidine (35). Furalazine, acetylfuratrizine (36), and the *N-N*-bis(hydroxymethyl) derivative, Panfuran-S, formed from the parent compound and formaldehyde (37), are systemic antibacterial agents.

Nifuroxime. The anti form of the oxime prepared from 5-nitro-2-furancarboxaldehyde and hydroxylamine, has been marketed for topical use as an antibacterial or an antifungal agent (1,17).

Nitrofurazone. 2-[5-Nitro-2-furanyl)methylene]hydrazinecarboximide, the first nitrofuran to be employed clinically, is prepared from 5-nitro-2-furancarboxaldehyde and semicarbazide (19). This product has seen clinical use topically as an antibacterial, for systemic application for bacterial infections in poultry and swine, and also has been employed as a food additive. In rats, nitrofurazone is hydroxylated at the 4 position of the furan moiety (27). The involvement of nitrenium ions has also been postulated in the mechanism of action of nitrofurazone (38).

Nifuraldezone. Aminooxoacetic acid [(5-nitro-2-furanyl)methylene]-hydrazide, nifuraldezone, is prepared by the reaction of 5-nitro-2-furancarboxaldehyde with semioxamazine. The product is useful in the treatment of dysentery in calves (39).

Nihydrazone. Acetic acid [5-nitro-2-furanyl)methylene]-hydrazide has seen use in veterinary medicine both as a coccidiostat and an antibacterial (39).

Nitrofurantoin. The urinary tract antibacterial, 1-[(5-nitro-2-furanyl)-methyleamino]-2,4-imidazolidinedione, is prepared by reaction of 5-nitro-2-furancarboxaldehyde with 1-amino-2,4-imidazolidinedione (19,40). Crystallization of the material from nitromethane provides a macrocrystalline form (41) which continues to be employed clinically.

In rats, the oxidative and reductive metabolism products have been identified as the 4-hydroxylated furan and [(3-cyano-1-oxopropyl)methyleamino]-2-4-imidazolidinedione, respectively (27,42). In addition, the ease of electron transfer as a mechanism of activity with nitrofurantoin and nitrofurazone has been studied (43).

Nifuratel. Nifuratel, 5-[(methylthio)methyl]-3-[5-nitro-2-furanyl)-methyleamino]-2-oxazolidinone, is prepared by treatment of the appropriate methyl-thiohydrazinopropanol with diethylcarbonated followed by condensation with 5-nitro-2-furancarboxaldehyde diacetate (44). The product has been used in antibacterial, antifungal, and antiprotzoal applications.

Nitrofurathiazide. 6-Acetylamino-3,4-dihydro-3-(5-nitro-2-furanyl)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, nitrofurathiazide, is synthesized from 4-acetylamino-2-aminobenzenesulfonamide with 5-nitro-2-furancarboxaldehyde (45). The product has been employed as an antibacterial agent for humans and, in combination with other drugs, has been used for acute or chronic otitis externa of dogs and cats.

Nifurtoinol. Treatment of nitrofurantoin with formaldehyde gives nifurtoinol, 3-hydroxymethyl-1-[5-nitro-2-furanyl)methyleamino]-2,4-imidazolidinedione, a urinary tract antibacterial (46). The kinetics of decomposition of this drug and its potential as a prodrug of nitrofurantoin have been reported (47).

Nifurprinol. 6-[2-(5-Nitro-2-furanyl)ethenyl]-2-pyridine methanol, is prepared from 5-nitro-2-furancarboxaldehyde and 6-methyl-2-pyridine methanol (48). The product has been used as an antibacterial in fish diseases.

Additional discussions are available in the General References concerning the properties of several nitrofurans. This includes further coverage of the chemotherapeutic and physical properties; antimicrobial activity; bacterial resistance; absorption, distribution, and excretion; clinical use; and safety studies, of this interesting class of antiinfective compounds.

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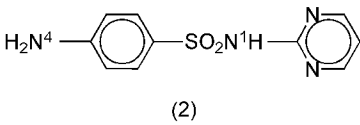
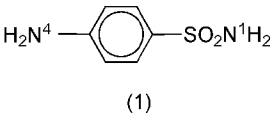
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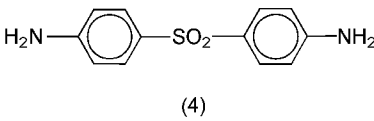
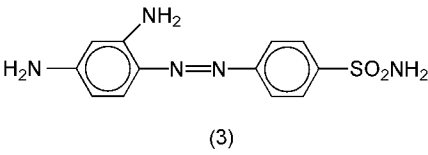
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SULFONAMIDES

Sulfonamides derived from sulfanilamide (*p*-aminobenzenesulfonamide) are commonly referred to as sulfa drugs. Although several drug classes are characterized by the presence of a sulfonamide function, eg, hypoglycemics, carbonic anhydrase inhibitors, saluretics, and tubular transport inhibitors, the antibacterial sulfonamides have become classified as the sulfa drugs. Therapeutically active derivatives are usually substituted on the N¹ nitrogen; the N⁴ position is generally unsubstituted. These features are illustrated by the structures of sulfanilamide (1) and sulfadiazine (2)



Some related antibacterials are also included with the sulfonamides. The azo dye, Prontosil (3) is metabolized to sulfanilamide *in vivo*, and was the progenitor of the sulfa drugs. Also, the antibacterial sulfones, eg, dapsone (4), are believed to act in a similar fashion on enzymes involved with synthesis of folic acid, leading to bacterial growth inhibition.



A monograph (1) covers the pioneering period of sulfa drug development and describes over 5000 sulfanilamide derivatives, their preparation, properties, trade names, and biological testing. This review is remarkably complete through 1944. Several thousand additional derivatives have been made since, but no comparable coverage is available. A definitive account of medical applications up to 1960 has been published (2), and a review of experimental antibacterial aspects has been made (3). Chapters on general aspects of sulfonamides and sulfones have appeared (4,5). A review of the clinical efficacy of trimethoprim–sulfamethoxazole has been published (6).

The sulfa drugs are still important as antimicrobials, although they have been replaced in many systemic infections by the natural and semisynthetic antibiotics. They are of great value in third world countries where problems of storage and lack of medical personnel make appropriate use of antibiotics difficult. They are especially useful in urinary tract infections, particularly the combination of sulfamethoxazole with trimethoprim. Their effectiveness has been enhanced by co-administration with dihydrofolate reductase inhibitors, and the combination of sulfamethoxazole with trimethoprim is of value in treatment of a number of specific microbial infections. The introduction of this combination (cotrimoxazole) in the late 1960s (1973 in the United States) resulted in increased use of sulfonamides.

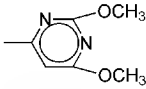
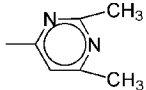
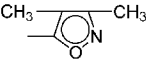
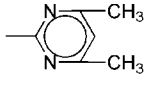
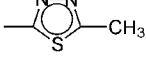
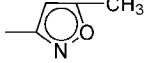
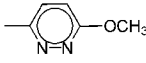
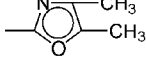
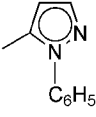
The sulfas also remain clinically useful in the treatment of chancroid, lymphogranuloma venereum, trachoma, inclusion conjunctivitis, and the fungus-related nocardiosis (7). In combination with pyrimethamine, they are recommended for toxoplasmosis (8) and have been used for chloroquine-resistant falciparum malaria (4,9). There has also been some use of sulfas for the prophylaxis of rheumatic fever. The sulfone, dapsone, remains an accepted treatment for all forms of leprosy (4).

The clinical usefulness of the sulfonamides depends not only on antimicrobial effectiveness, but on other factors such as aqueous and liposolubility, protein-binding, half-life, and metabolism. Currently used sulfas vary widely in their absorption, distribution, and excretion patterns. Some of those in clinical practice, past or present, are listed in Tables 1 and 2. These can be grouped according to their rate of absorption and half-life. One group remains largely unabsorbed after oral administration, and is useful for gastrointestinal infections. A second group is characterized by high solubility, quick absorption, and rapid excretion, mainly unaltered, and is widely used for urinary tract infections. Another group is absorbed rapidly but excreted slowly, maintaining adequate blood levels for long periods; these drugs are useful for chronic infections and for prophylaxis. Sulfonamides with half-lives up to 10 h are considered short-acting, those with half-lives of 10–24 h are termed medium-acting, and those with half-lives of longer than 24 h are long-acting. This wide range of pharmacokinetic properties, along with their ease of administration, broad spectrum antimicrobial activity, and noninterference with host-defense mechanisms is responsible for their widespread use five decades after their discovery.

R'N^4H-c1ccc(cc1)S(=O)(=O)N^1HR

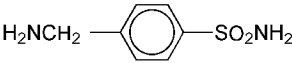
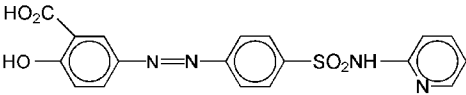
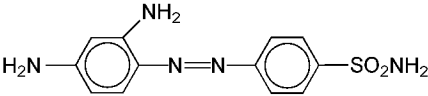
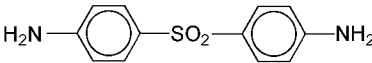
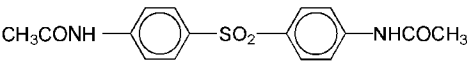
Table 1. Sulfonamides of Structure

Generic name	R	CAS Registry Number	pK _a	Solubility in water, 25°C, mg 100 mL	Liposolubility, _o / _o ^a	Human plasma half-life ^a , h	Protein binding ^b % bound
<i>R'</i> = H							
sulfanilamide	H	[16-74-1]	10.5	750	71	9	9
sulfacetamide	COCH ₃	[144-80-9]	5.4	>670	2.0	7	9.5
sulfadiazine		[68-35-9]	6.5	8	26.4	17	37.8

							
sulfadimethoxine		[122-11-2]	6.1	<4.6	78.7	40	92.3
sulfaguanidine	—C(NH)NH ₂	[57-67-0]	12.05	100		5	
sulfisomidine		[515-64-0]	7.4	~200	19	7.5	67
sulfisoxazole		[127-69-5]	5.0	350 ^c	4.8	6	76.5
sulfamethazine		[57-68-1]	7.4	~100	82.6	7	66
sulfamethizole		[144-82-1]	5.5	25		2.5	22
sulfamethoxazole		[723-46-6]	6.0		20.5	11	60
sulfamethoxypyridazine		[80-35-3]	7.2	110 (pH5)	70.4	37	77
sulfamoxole		[729-99-7]	7.4	85	41.4	11	76.5
sulfaphenazole		[526-08-9]	6.1	150	69	10	87.5
sulfapyridine		[144-83-2]	8.4	30	14	9	70
sulfapyrazine		[116-44-9]	6.0	5			
sulfathiazole		[72-14-0]	7.25	60	15.3	4	68
<i>R'</i> phthalyl N ⁴ -phthalylsulfathiazole		[85-73-4]	acid	sol (pH7)			
<i>R'</i> succinyl N ⁴ -succinylsulfathiazole		[116-43-8]	acid	20			

^a Ref. 4, pp. 28–31.
^b At 1.0 μmol mL.
^c *N'*-acetylsulfisoxazole [80-74-0] water solubility 7 mg 100 mL.

Table 2. Sulfones and Other Structures Related to Sulfonamides

Generic name	Structure	CAS Registry Number	Solubility in water, 25°C mg /100mL	Human plasma half-life ^a
mafenide		[138-39-6]	sol (salt)	
sulfasalazine		[599-79-1]	sol (pH7)	
sulfamidochrysoidine (Prontosil)		[103-12-8]	sol (salt)	
dapsone ^b		[80-08-0]	insol	20 h ^c
acedapson		[77-46-3]	0.3	43 d ^d

^a Ref. 4, pp. 28–31.
^b p*K_a* of protonated form 1.3.
^c Protein binding at 1.0 μmol /mL 50% bound.
^d Intramuscularly.

Their antimicrobial activity includes species requiring a folic acid synthetic pathway, comprising many gram-positive and gram-negative cocci and bacilli, mycobacteria, some large viruses, protozoa, and fungi (5). The action of the sulfa drugs and related sulfones is bacteriostatic rather than bactericidal. It is believed to be due to interference with the assembly of folic acid at the step that adds *p*-aminobenzoic acid (PABA). For a thorough discussion of the mechanisms of action postulated for the sulfonamides, see reference 10.

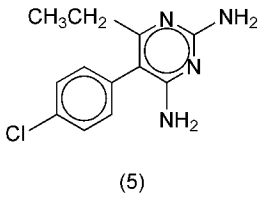
The discovery of the sulfa drugs, the first to control systemic bacterial infections, had its origin in the investigation of organic dyes for chemotherapeutic purposes initiated by Paul Ehrlich and others in the first decade of the 1900s. The azo compound, Prontosil [103-12-8] (3), was discovered at the I. G. Farbenindustrie in Germany in 1935 (11) to cure bacterial septicemias. It was fortunate that animal tests were used in the screening procedure, because Prontosil (sulfamidochrysoidine) is inactive *in vitro*. A group at the Pasteur Institute in Paris found that sulfanilamide, a metabolic product, was responsible for the activity (12), and was active against susceptible organisms both *in vitro* and *in vivo* (12,13). This marked the beginning of a worldwide effort to prepare and test derivatives and analogues of sulfanilimide. In less than 10 years, over 5000 compounds of this type were synthesized, and they appear in the 1948 review (1). The effort to find compounds having a broader antimicrobial spectrum and improved therapeutic ratio resulted in the development and clinical use of the *N*¹-heterocyclic substituted sulfanilamides, exemplified by sulfapyridine, sulfathiazole, and sulfadiazine (all 2-substituted heterocycles). Later research has not produced sulfonamides having greater activity, but compounds having improved pharmacokinetic properties for specific uses have largely replaced the first used sulfonamides.

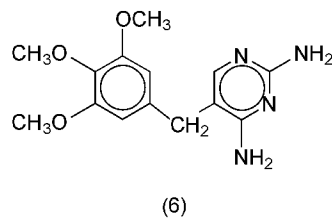
During the most active period of investigation of sulfanilamide derivatives, 1935–1944, for systemic bacterial infections, the antimycobacterial activity of 4,4'-diaminodiphenylsulfone [80-08-8] (DDS, dapsone) was discovered (14). Although neither this compound nor its derivatives proved to be clinically useful for human tuberculosis, it did evolve into the most important type of compound for leprosy (15). The *N,N'*-diacetyl derivative has also found use against certain resistant strains of falciparum malaria.

Therapeutic Aspects

Systemic Infections. The sulfonamides were the first drugs effective against the bacterial septicemias (blood stream infections), but they have also been effective in tissue infections due to streptococci, and fungus-related nocardia (2). However, penicillin and other natural and semisynthetic antibiotics have displaced the sulfas for many uses. The sulfas continue to be used in such conditions as rheumatic fever prophylaxis and in nocardiosis (16). Sodium sulfacetamide solution or ointment is also used in infections of the conjunctiva, and oral administration of the insoluble sulfonamides, phthalyl or succinyl sulfathiazole, phthalyl sulfacetamide, and sulfaguanidine, provide temporary inhibition of the intestinal microbial flora. This is of value in preparing the bowel for surgery (17). Topical use of sulfonamides is generally unsatisfactory and is accompanied by a high risk of allergic sensitization.

Sulfonamides in combination with dihydrofolate reductase inhibitors are of continuing value. Pyrimethamine [58-14-0] (5) in combination with sulfonamides is employed for toxoplasmosis (7), and a trimethoprim (6)-sulfamethoxazole preparation is used not only for urinary tract infections but also for brucellosis, cholera, and malaria.





Synergistic effects are accomplished by the use of these combinations. Resistance to this combined therapy, either by bacteria or protozoa, emerges very slowly (18).

Urinary Tract Infections. The sulfa drugs have maintained an important place in treatment of urinary tract infections, where short acting, highly soluble drugs are required (19). Those most used in the United States are sulfisoxazole, sulfamethizole, sulfisomidine, and sulfacytine. For chronic urinary tract infection, the sulfamethoxazole–trimethoprim combination is frequently employed.

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid, and trimethoprim blocks the production of tetrahydrofolic acid by inhibiting the enzyme dihydrofolate reductase. Thus two consecutive steps are blocked in the biosynthesis of nucleic acids and proteins essential to many bacteria. *In vitro* serial dilution tests have shown that the combination of sulfamethoxazole and trimethoprim [738-70-5] inhibits the growth of common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. Table 3 illustrates the enhanced effect of the combination over that of either agent alone.

Table 3. Representative Minimum Inhibitory Concentrations^a for Urinary Tract Organisms by Sulfamethoxazole (SMX), Trimethoprim (TMP), and Their Combination

Bacteria	TMP alone	SMX alone	Combination ^b of TMP and SMX	
			TMP	SMX
<i>Escherichia coli</i>	0.05–1.5	1.0–245	0.05–0.5	0.95–9.5
<i>Proteus</i> spp., indole +	0.5–5.0	7.35–300	0.05–1.5	0.95–28.5
<i>Proteus mirabilis</i>	0.5–1.5	7.35–30	0.05–0.15	0.95–2.85
<i>Klebsiella-Enterobacter</i>	0.15–5.0	2.45–245	0.05–1.5	0.95–28.5

^a MIC in µg mL.

^b TMP: SMX = 1 : 20.

Mixtures of sulfas (eg, the tri-sulfapyrimidines) have also been used for this purpose. Resistant organisms frequently result after a urinary tract infection has been treated with sulfonamides, however.

Other Infections. The slowly excreted sulfonamides (eg, sulfamethoxypyridazine, sulfadimethoxine) are used for treatment of minor infections such as sinusitis or otitis, or for prolonged maintenance therapy. Soluble sulfonamides are sometimes used for protozoal infections in combination with other agents. Pyrimethamine, combined with sulfonamides, has been used for toxoplasmosis or leishmaniasis, and trimethoprim with sulfonamides has been used in some types of malaria. In nocardiosis, sulfonamides have been used with cycloserine [68-41-7] (17).

Resistance to sulfonamides is now common for *N. meningitidis*, as well as in cases of bacillary dysentery. Antibiotics have generally replaced the sulfonamides for these purposes. Sulfonamides, particularly sulfisoxazole and sulfadiazine, are of value in treatment of infections due to *Nocardia* species, and sulfonamides are effective for trachoma. Inclusion conjunctivitis is also treated with sulfacetamide ointment. Oral administration of a sulfonamide, eg, sulfisoxazole, has been successful for treatment of lymphogranuloma venereum and chancroid. Dapsone and sulfonamides have also been used for treatment of the skin disorder dermatitis herpetiformis. Sulfonamides have been used for long term prophylaxis of rheumatic fever, but are being replaced by penicillin for this purpose, except in cases of hypersensitivity to penicillin (19).

Because of several unique properties, the sulfonamides continue to occupy an important place in antimicrobial therapy. Development of derivatives that remain largely unabsorbed in the intestinal tract makes them of particular advantage in causing local changes in the bacterial flora. Development of sulfas with high solubility in the urine and low renal toxicity has provided agents with effectiveness in chronic urinary tract infections. Also, the establishment of the value of sulfonamide combinations with the dihydrofolate reductase inhibitors trimethoprin and pyrimethamine has given the sulfas a preferred place in management of some specific microbial infections.

Physiochemical Properties

The sulfa drugs are weak acids, the more important ones generally having a p*K_a* in the range of 5–8. This acidity, due to the sulfonamide function, makes the sulfas soluble in basic aqueous solution. The p*K_a* is modified by the presence of the *N*¹-substituent, but the clinically useful sulfas generally have p*K_a* values which give the compounds good solubility at physiologic pH. The *N*⁴-acyl derivatives, such as succinylsulfathiazole, phthalylsulfathiazole, and salicylazosulfapyridine, contain a free carboxyl group and are soluble in the physiologic pH range. As pH is lowered, the solubility of the *N*¹-substituted sulfonamides reaches a minimum in the range of pH 3–5, which corresponds to the solubility of the molecular species. At this pH, either the sulfa molecule or its *N*⁴-acetyl metabolic product may crystallize in the kidneys, giving rise to blockage and irritation. Because most of the sulfas have a free aromatic amino group which can be protonated, the sulfas are soluble as cations with p*K_s* of ~2. Both their aqueous and liposolubilities have been thoroughly studied (20–22).

The amino group is readily diazotized in aqueous solution, and this reaction forms a basis for the assay of sulfas. Aldehydes also react to form anils, and the yellow product formed with 4-(dimethylamino)benzaldehyde can be used for detection in thin-layer and paper chromatography. Chromatographic retention values have been determined in a number of thin layer systems, and have been used as an expression of the lipophilic character of sulfonamides (23). These values have corresponded well with Hansch lipophilic parameters determined in an isobutyl alcohol–water system.

Lipid solubilities of the sulfonamides vary over a wide range. Oil–water partition coefficients using an aqueous ethylene chloride system have been determined (20). The differences among individual members unquestionably influence their pharmacokinetics as well as antimicrobial activity. The longer acting sulfonamides with high tubular reabsorption generally have a high degree of liposolubility (19). Both antimicrobial activity and half-life of the drug are influenced by liposolubility, but these effects cannot be separated from that of the degree of ionization at physiologic pH, so no precise relation between activity and liposolubility has been established.

Numerous studies have been made to find a correlation between the physicochemical properties of the sulfonamides and their bacteriostatic activity. Degree of ionization, lipid–water solubility, and protein binding have all been observed. The presence of a primary aromatic amino group has been found essential for activity, and the presence of *N*¹-substituents is a significant influence in the degree of acid dissociation of the sulfonamide group. As early as 1942, a study of the relationship between the p*K_a* and antibacterial activity of an extensive series of sulfonamides showed that a plot of log 1/MIC against p*K_a* was a parabolic curve, the maximum lying between p*K_a* 6.0 and 7.4 (24). The maximal activity was thus observed in compounds with a p*K_a* that fell in the physiologic pH range. The p*K_a* of most of the active sulfonamides found since then has been in this range as well. These findings (24) were related to the antimetabolite theory (25,26), regarding the structural similarity between the sulfonamide and the natural substrate, PABA, that it was replacing. The

theory emphasized the need for polarization of the sulfonyl group, so that it should resemble as closely as possible the geometrical and electronic characteristics of the *p*-aminobenzoate ion.

In another attempt to relate degree of ionization with antibacterial activity, the effect of pH of the medium on the antibacterial activity was studied (27,28). Activity increased with increase in pH only up to the point at which the drug was 50% ionized, and then decreased. The interpretation of this was that sulfonamides penetrate the bacterial cell in the unionized form, but once inside the cell, the equilibrium between ionized and unionized forms is reestablished, and the activity is due to the ionized form. For optimum activity, a sulfonamide should have a pK_a that provides half-dissociation at the physiologic pH in the area where it is absorbed. This observation also provided an explanation of the parabolic relationship between pK_a and MIC (24).

In subsequent studies attempting to find a correlation of physicochemical properties and antimicrobial activity, other parameters have been employed, such as Hammett σ values, electronic distribution calculated by molecular orbital methods, spectral characteristics, and hydrophobicity constants. No new insight on the role of physiochemical properties of the sulfonamides has resulted. Acid dissociation appears to play a predominant role, since it affects aqueous solubility, partition coefficient and transport across membranes, protein binding, tubular secretion, and reabsorption in the kidneys. An exhaustive discussion of these studies has been provided (10).

Biological Mechanism of Action

The sulfa drugs act on microorganisms by limiting or halting growth rather than by a bactericidal action. They inhibit growth of bacteria *in vitro* only if the medium is free of inactivating substances, mainly peptones and *p*-aminobenzoic acid. If *in vitro* activity had been a prerequisite for testing as a drug, neither Prontosil nor sulfanilamide itself would have been selected.

The Woods-Fildes theory postulated that *p*-aminobenzoic acid (PABA) [150-13-0] is an essential metabolite for the bacteria that are affected. Woods obtained evidence that PABA antagonizes the activity of sulfonamides and showed that PABA could completely reverse the bacteriostatic activity of sulfanilamide against various bacteria *in vitro*. PABA was later isolated from the various tissues and fluids, and yeast extract, where antagonism to sulfanilamide was found. Further studies showed that inhibition of bacterial growth by sulfonamides in simple media can be reversed not only competitively by PABA, but also noncompetitively by compounds not structurally related to PABA, such as 1-methionine, 1-serine, glycine, adenine, guanine, and thymine (29). The finding that sulfanilamide-inhibited cultures accumulated 4-amino-5-imidazolecarboxamide ribotide (30), a precursor to purine biosynthesis (31), indicated that purine biosynthesis was affected by the sulfonamides.

The primary mode of action of the sulfonamides is, however, the interference with the uptake of PABA for the formation of folic acid [59-30-3]. The sulfonamides impede this synthesis and are therefore toxic to those bacteria that synthesize their own folic acid. Mammals cannot synthesize this and related vitamins and depend on food sources for them; the sulfas are therefore not toxic to mammals in this regard.

Subsequent knowledge of the structure, function, and biosynthesis of the folic acid coenzyme gradually allowed a picture to be formed regarding the step in this pathway that is inhibited by sulfonamides. The biosynthetic scheme for folic acid is shown in Figure 1. Sulfonamides compete in the step where condensation of PABA with pteridine pyrophosphate takes place to form dihydropteroate (32). The amino acids, purines, and pyrimidines that are able to replace or spare PABA are those with a formation that requires one-carbon transfer catalyzed by folic acid coenzymes (5).

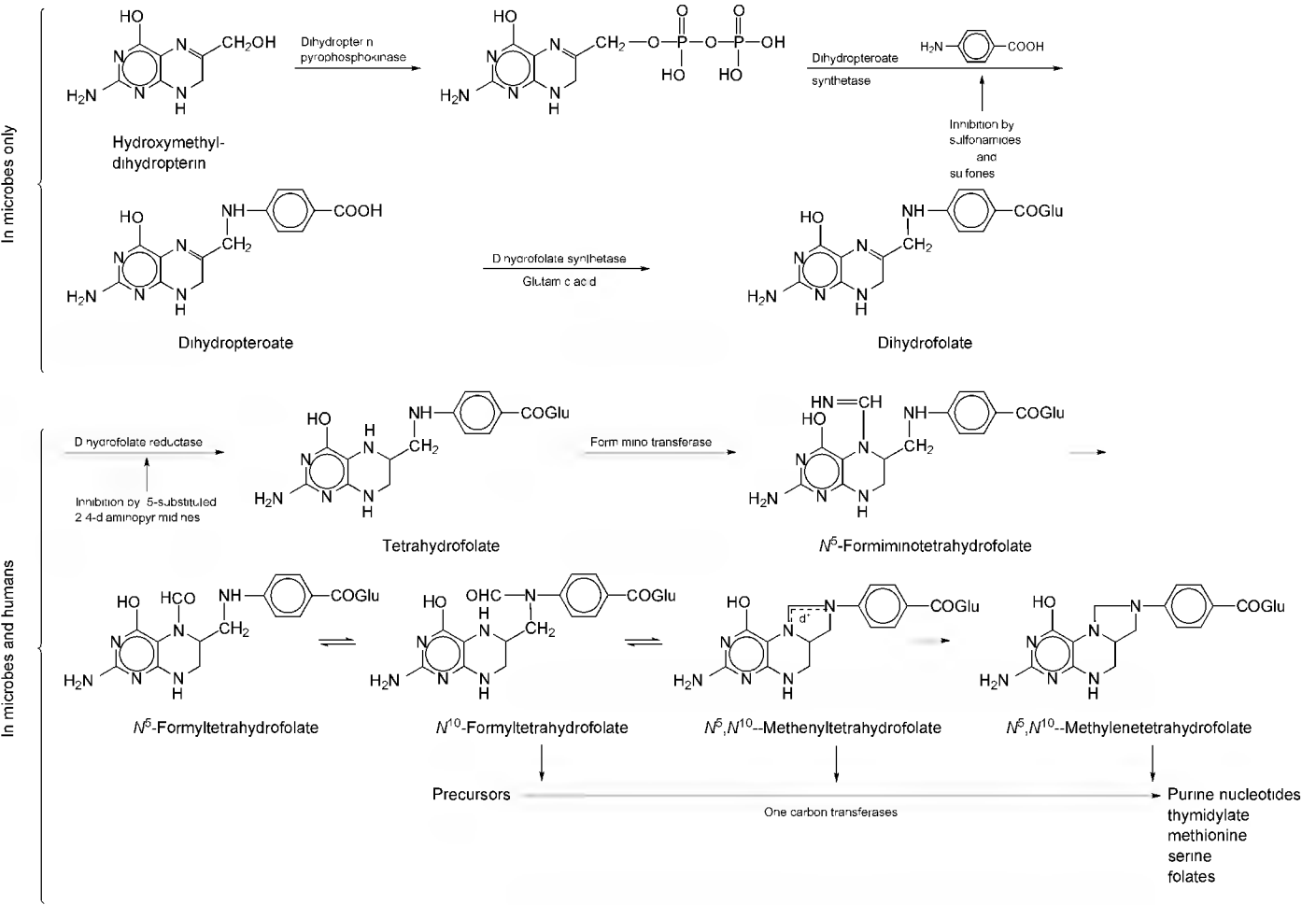


Fig. 1. Folate metabolism and sites of action of antifolates.

Courtesy of Lea & Febiger (5).

Direct evidence of the inhibition of dihydropteroate and dihydrofolate synthesis was obtained (33) from work with enzymes from *E. coli*. The synthesis of dihydropteroate from PABA is inhibited by a number of sulfonamides and, in general, the more potent inhibitors of folate biosynthesis are the better bacterial growth inhibitors. Subsequently, evidence was obtained of incorporation of sulfonamides (34,35) in the pteridine moiety, but this incorporation is probably not of physiologic significance (36). Two binding sites on the enzyme involved, dihydropteroate synthetase, have been proposed (37) as being involved in the competition between PABA and the sulfonamides. One is specific for the NH₂ group, and the other is where the acidic group of PABA, or the SO₂ function of the sulfonamide, binds. This view of the inhibition accommodates both sulfonamides and sulfones, since the sulfonamide NH is not a binding function. The present knowledge of the topography of the enzyme surface is not sufficient to explain how the additional phenyl group

of the sulfones is accommodated, but it is likely that there is sufficient bulk tolerance for this group as well as the N^1 -heterocycles of the sulfonamides. Competition with PABA for these binding sites is most likely the primary mode of action of the sulfonamides and sulfones (see reference 10 for a more complete discussion of this binding).

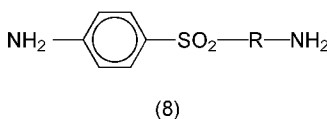
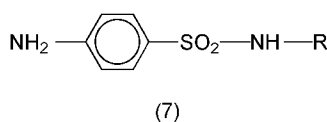
Development of Resistance. One of the principal disadvantages of sulfonamide therapy is the emergence of drug-resistant strains of bacteria. Resistance develops by several mechanisms: overproduction of PABA (38); altered permeability of the organisms to sulfonamides (39); and reduced affinity of dihydropteroate synthetase for sulfonamides while the affinity for PABA is retained (40). Sulfonamides also show cross-resistance to other sulfonamides but not to other antibacterials. In plasmodia, resistance may occur by means of a bypass mechanism in which the organisms can use preformed folic acid (41).

Structure-Activity Relationships

The following generalizations arose from a review of more than 5000 sulfonamides (1).

- (1) The amino and sulfonyl groups on the benzene ring should be in the 1,4 positions; the amino group should be unsubstituted or converted to a free amino *in vivo*.
- (2) Replacement of the benzene ring by other ring systems, or the introduction of additional substituents, decreases or abolishes activity.
- (3) Exchange of the SO_2NH by SOC H_4 - p - NH_2 , CONH_2 , CONHR , or COC H_4 R generally reduces activity.
- (4) N^1 -Monosubstitution may result in greater activity, and will increase activity with a number of heterocycles; N^1 -disubstitution in general leads to inactive compounds.

A later review (42) confirmed these generalizations. Replacement of the SO_2NH by $\text{SO}_2\text{C H}_4$ - p - NH_2 gives the sulfones that show reduced activity for some bacterial species, but show good activity against leprosy and some strains of malarial organisms. General structures summarizing the essential features for activity for the sulfonamides (7) and sulfones (8) follow.

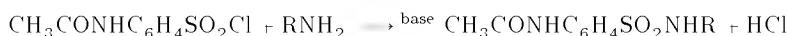


For the sulfonamides, the best activity is found where R is heterocyclic, but it can also be isocyclic or acyl. For the sulfones, R can be phenylene or a heterocycle; the parent dapsone, where R is phenyl, is the most active.

Other related structures may be active, but through a different mechanism. Separation of the amino group from the ring by CH_2 has provided an active sulfonamide, mafenide. Replacement of the amino by amidino has also given an active sulfone, methyl *p*-aminodiphenyl sulfone [17574-50-4], for which no metabolite antagonist is known (1). Although not a sulfonamide, *p*-aminosalicylic acid [65-49-6] also has its action reversed by PABA. It has bacteriostatic action, but is most specific against mycobacteria (43).

Preparation and Manufacture

The most common method for the preparation of sulfonamides is by the action of *N*-acetylsulfanilyl chloride with the appropriate amine (1). Excess amine or suitable base is used to neutralize the hydrochloric acid formed.

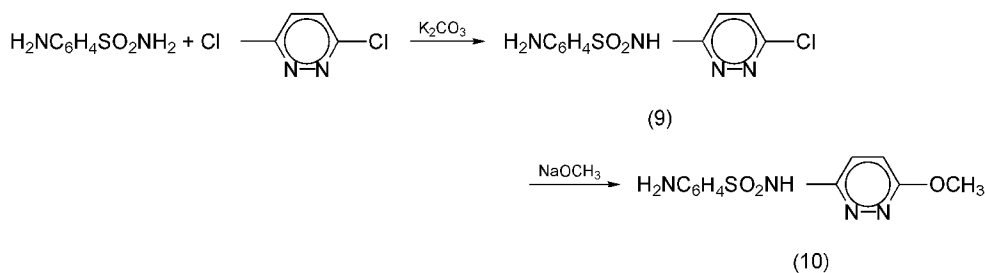


The resulting acetyl compound is usually hydrolyzed with aqueous alkali to give the free amine. Other *N*-acyl derivatives may be used, particularly for the less soluble succinyl and phthaloyl products. The use of *p*-nitrobenzenesulfonyl chloride, followed by reduction of the nitro to an amino function, is much more expensive and is rarely used. *N*-Acetylsulfanilyl chloride [121-60-8] is obtained by the chlorosulfonation of acetanilide [103-84-4], which is the basic material for most of the sulfonamides.

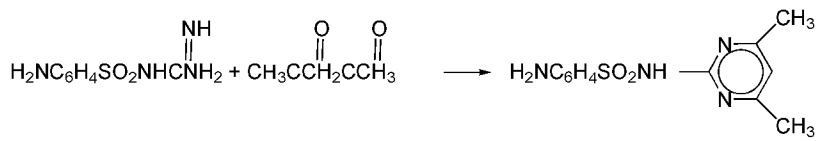
N^1 -Heterocyclic Sulfanilamides. The parent sulfanilamide is manufactured by the reaction of *N*-acetylsulfanilyl chloride with excess concentrated aqueous ammonia, and hydrolysis of the product. Most heterocyclic amines are less reactive, and the condensation with the sulfonyl chloride is usually done in anhydrous media in the presence of an acid-binding agent. Use of anhydrous conditions avoids hydrolytic destruction of the sulfonyl chloride. The solvent and acid-binding functions are commonly filled by pyridine, or by mixtures of pyridine and acetone. Tertiary amines, such as triethylamine, may be substituted for pyridine. The majority of N^1 -heterocyclic sulfanilamides are made by simple condensation with *N*-acetylsulfanilyl chloride and hydrolysis.

A variation of this procedure is used for sulfisomidine because of the different character of the amino group in the 4-position of a pyrimidine ring. Two moles of the sulfonyl chloride are condensed with one mole of 4-amino-2,6-dimethylpyrimidine in the presence of triethylamine. The resulting bis(acetylsulfanilyl) derivative is readily hydrolyzed to the product. The formation of the bis(acetylsulfanilyl) derivative has also been employed for other heterocyclic amines, eg, for synthesis of sulfathiazole and sulfamoxole (44), but the 1:1 reaction is probably preferable.

In a few cases, N^1 -heterocyclic sulfanilamides have been prepared by the condensation of an active heterocyclic halide with the sulfonamide nitrogen of sulfanilamide or its *N*-acetyl derivative in the presence of an acid-binding agent. Sulfapyridine, sulfadiazine, and sulfapyrazine have been made by this method (1), but the most important application is probably for the synthesis of sulfachlorapyridazine (9) and sulfamethoxyypyridazine (10) (45).



N^1 -Heterocyclic derivatives can be formed in some cases by a ring closure to give the heterocycle. Sulfadiazine, sulfamethazine, sulfamerazine, and sulfathiazole have been prepared in this fashion, but also by the usual procedure from the sulfonyl chloride and heterocyclic amine. The synthesis of sulfamethazine from sulfaguanidine is an example of the ring closure method.



N⁴-Acylsulfanilamides. Only two examples of this class still have much use in the United States. Sulfacetamide is prepared by acetylation of N⁴-acetylsulfanilamide in pyridine. The resulting N¹, N⁴ diacetylsulfanilamide can be hydrolyzed selectively with alkali to give the monacetyl product. Its separation from regenerated sulfanilamide is easily achieved because of the greater acidity of sulfacetamide. Sulfabenzamide may be prepared in similar fashion.

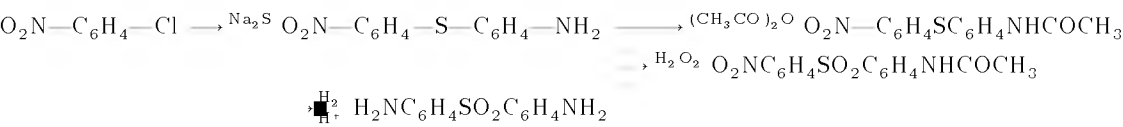
Sulfaguanidine is prepared by condensation of N-acetylsulfanilyl chloride with guanidine in presence of alkali. The N⁴-acetyl group is removed by acid or alkaline hydrolysis.

N-Heterocyclic-N⁴-acylsulfanilamides. Two examples of this class still in use are succinylsulfathiazole and phthalylsulfathiazole. They are prepared by fusion of sulfathiazole with appropriate anhydrides.

N-Heterocyclic-N¹-acetylsulfanilamides. These derivatives may be prepared by condensation of the heterocyclic amine with p-nitrobenzenesulfonyl chloride followed by acetylation of the nitro compound. The product may be reduced under mild conditions to give the 4-amino-N¹-heterocyclic-N¹-acetyl derivative. Other approaches, however, have been developed (46,47).

Other Derivatives. Salicylazosulfapyridine [599-79-1] (sulfasalazine) can be prepared by diazotization of sulfapyridine and coupling to salicylic acid. Mafenide is prepared by chlorosulfonating N-benzylacetamide, reaction of the resulting α-acetamido-p-toluenesulfonyl chloride with ammonia, and hydrolyzing the acetyl group.

Dapsone has been prepared by a number of procedures (1,48). One procedure employs the reaction of 1-chloro-4-nitrobenzene with excess sodium sulfide to give the 4-amino-4'-nitrodiphenyl sulfide. This compound, after acetylation of the amino group, is oxidized with H₂O₂ to the sulfone. The nitro group is then reduced to amino, and hydrolysis of the acetyl gives the product.



Analysis

Sulfonamides having a free p-amino group are readily assayed by titration with nitrous acid. The sulfonamide function may also be titrated with base, such as lithium methoxide. The majority of the sulfas listed in the U.S. Pharmacopeia XXII, however, are assayed by chromatographic methods, particularly high performance liquid chromatography (49). Sulfonamides for which assays are listed in the U.S. Pharmacopeia XXII-National Formulary XVII include the following: sulfacetamide, sulfabenzamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethazine, sulfamethazole, sulfamethoxazole, sulfapyridine, sulfasalazine, sulfathiazole, sulfinpyrazone, sulfisoxazole, sulfisoxazole acetyl, sulfisoxazole diolamine, sulfoxone, triple sulfa, dapsone, and various combinations with prednisolone, pyrimethamine, and trimethoprim.

Toxicity

A small percentage of patients treated with sulfa drugs have shown toxic effects, such as drug fever, rashes, mild peripheral neuritis, and mental disturbance. In general, these effects are more prevalent with higher blood levels, and may accompany poor excretion or overdosing (21). In 1966 the FDA required that two long-acting sulfas, sulfamethoxypyridazine and sulfadimethoxine carry a label warning of the possibility of death due to Stevens-Johnson syndrome, an extremely severe dermatologic reaction (50).

Crystalluria, due to formation of insoluble N-acetyl metabolic products, was one of the more serious toxic effects observed with sulfonamide therapy. This is much less of a problem than with the early sulfas, mainly because of the discovery of agents highly soluble at urinary pH, the development of long-acting sulfas that build up adequate blood levels at doses low enough to avoid crystallization, and the discovery of compounds that are excreted chiefly as highly soluble glucuronides. The danger of kidney blockage is also reduced by increasing fluid intake and by administering sodium bicarbonate to alkalinize the urine. The use of mixtures, such as triple sulfa, also reduces the possibility of crystallization in the kidneys.

Blood dyscrasias are quite uncommon, but if they occur may be serious enough to cause discontinuance of the therapy. Both topical and systemic administration of sulfas can cause hypersensitivity reactions, such as urticaria, exfoliative dermatitis, photosensitization, erythema nodosum, and in its most severe form, erythema multiformexudativum. (Stevens-Johnson syndrome). In general, however, use of sulfonamide therapy is considered relatively safe.

Economic Aspects

The production of sulfa drugs increased rapidly after their introduction in the 1930s, and reached a maximum of 9000 t in 1943. An abrupt drop to less than half this amount occurred in 1944, with the commercial availability of penicillin. Contrary to some expectations that the sulfas would be totally replaced by antibiotics, their output has remained close to the 1944 level. Increased veterinary use, along with low cost and effectiveness of the sulfas has maintained a market for them. United States production figures of sulfas for selected years are shown in Table 4, in comparison with those for total antibiotics. The most recent figures released for sulfa drugs also include those for other agents, such as antiprotozoan agents and other urinary tract antiinfective agents.

Table 4. United States Production of Sulfa Drugs and Antibiotics, t^a

Drug	1943	1946	1956	1966	1975	1987
total sulfa drugs	9077	4630	3462	4944	2122	5557 ^b
total antibiotics	0	34.5	1784	8756	8312	16,099

^a From Ref. 51.
^b Also includes antiprotozoan agents and other urinary tract antiinfectives, but does not include the antileprotic sulfones.

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ANTIBIOTICS

Survey,
Aminoglycosides,
Ansamacrolides,
Chloramphenicol and analogues,
Erfamycins,
Glycopeptides,
β-Lactams,
Lincosaminides,
Macrolides,
Nucleosides,
Oligosaccharides,
Peptides,
Polyenes,
Polyethers,
Tetracyclines,

SURVEY

Antibiotics are chemical substances produced by microorganisms and other living systems that are capable in low concentrations of inhibiting the growth of bacteria or other microorganisms. This inhibitory effect can be *in vitro* or *in vivo*. Antibiotics having both *in vivo* activity and low mammalian toxicity have been extremely valuable in treating infectious diseases. There are over 10,000 antibiotics produced by microorganisms that have been reported in the scientific literature, approximately 6100 of which have been characterized and have had molecular structures assigned (1,2). These substances range from the very simple to extremely complex, but most antibiotics are in the 300–800 mol wt range. Many thousands of semisynthetic variations of the naturally occurring antibiotics have been prepared. Only relatively few (~200) have become commercial products for human and veterinary uses (see also ANTIBACTERIAL AGENTS).

Microorganisms producing antibiotics include antinomyces, fungi, bacteria, and algae. Marine organisms such as sponges and soft corals have also been found to produce antibiotics (3). In some cases symbiotic microorganisms such as algae may be responsible for the antibiotic production noted in the higher life forms. Terrestrial plants have also been found to produce some antibiotic substances (4).

The mechanism of action of a number of antibiotics with regard to the inhibition of bacteria, fungi, or other organisms has been established. The more common mechanisms include inhibition of bacteria cell wall biosynthesis, inhibition of protein, RNA, or DNA synthesis, and damaging of membranes (5). Cell wall biosynthesis is a target present in bacteria but not in mammalian cells. Thus the β -lactams, which are very effective against bacteria, are relatively nontoxic to humans. In contrast, antibiotics that damage DNA, like adriamycin, are relatively toxic to both types of cells. However, adriamycin, which was found to be more toxic to rapidly proliferating tumor cells than to most normal cells with slower turnover rates, shows significant selectivity against tumor cells to find clinical application as an antitumor agent (5).

History

Antibiotics were used in folk medicine at least as early as 2500 years ago when the Chinese reported the medicinally beneficial effects of moldy bean curd. Evidence for some type of tetracycline antibiotic usage by the Sudanese-Nubian civilization (350 AD) was reported in 1980 (6). Fluorescent areas in human bones from this era were observed that were identical in location and characteristics to modern bone from patients treated with tetracyclines. Identification of tetracycline in the ancient bones was further substantiated by fluorescence spectrum measurements and microbiological inhibition studies (7).

One of the most profound developments in the history of modern medicine has been the discovery of antibiotics to control infections. The realization that microbial products could cure infectious diseases spanned approximately sixty-five years of discoveries (8). One of the first modern scientific demonstrations was the observation by Louis Pasteur in 1877 that common bacteria inhibited the growth of a pure anthrax culture. Other observations followed. Then in 1928 it was noted by Alexander Fleming that a culture of a green *Penicillium* inhibited the growth of bacteria on an agar plate and in 1932 a paper on the use of the penicillin preparation as a topical agent for treating infected wounds was published. But it was not until 1940 that a systematic investigation of antibacterial substances was made along with a reinvestigation of the properties of penicillin. A stable dry powder was prepared from fermentations of *Penicillium* that possessed strong antibacterial properties and the clinical utility of penicillin, which was shown to be highly effective against bacterial infections yet nontoxic to animals, was clearly visible.

In 1939 the isolation of a mixture of microbial products named tyrothricin from a soil bacillus was described. Further investigation showed this material to be a mixture of gramicidin and tyrocidine. In rapid succession the isolation of actinomycin (1940), streptothricin (1942), streptomycin (1943), and neomycin (1949), produced by *Streptomyces*, were reported and in 1942 the word antibiotic was introduced. Chloramphenicol, the first of the so-called broad spectrum antibiotics having a wide range of antimicrobial activity, was discovered in 1947. Aureomycin, the first member of the commercially important tetracycline antibiotics, was discovered in 1948.

The number of naturally occurring antibiotics increased from about 30 known in 1945, to 150 in 1949, 450 in 1953, 1200 in 1960, and to 10,000 by 1990 (1,9). Table 1 lists the years of historical importance to the development of antibiotics used for treatment in humans. Most of the antibiotics introduced since the 1970s have been derived from synthetic modifications of the β -lactam antibiotics (qv).

Table 1. Year of Discovery or Market Introduction of Some of the More Important Antibiotics

Antibiotic	CAS Registry Number	Year	
		Discovery	Introduction
penicillin		1929	
tyrothricin	[1404-88-2]	1939	
griseofulvin	[1403-70-9]	1939	
streptomycin	[57-92-1]	1944	
bacitracin	[1405-87-4]	1945	
chloramphenicol	[56-75-7]		1947
polymyxin	[1406-11-7]	1948	
chlortetracycline	[57-62-5]		1948
Cephalosporin C,N,P		1948	
neomycin	[1404-04-2]	1949	
oxytetracycline	[79-57-2]		1950
nystatin	[1400-61-9]	1950	
erythromycin	[114-07-8]		1952
novobiocin	[303-81-1]	1955	
kanamycin	[8063-07-8]		1957
ampicillin ^a	[69-53-4]		1962
fusidic acid	[6990-06-3]		1961
cephalothin ^a	[153-61-7]	1962	
lincomycin	[154-21-2]		1963
gentamicin	[1403-66-3]		1963
carbenicillin ^a	[4697-36-3]	1964	
cephalexin ^a	[15686-71-2]	1966	
clindamycin ^a	[18323-44-9]		1967

cephalexidine and cephalothin ^{a,b}		1969
minocycline ^a	[10188-90-8]	1971
amoxycillin ^a	[26787-78-0]	1972
cefoxitin ^{a,c}	[35607-66-0]	1978
tricarcillin ^a	[34787-01-4]	1979
mezlocillin ^a	[51481-65-3]	1980
piperacillin ^a	[61477-96-1]	1980
cefotaxime ^a	[63527-52-6]	1980
moxalactam ^a	[64952-97-2]	1981
augmentin ^d	[74469-00-4]	1984
aztreonam ^e	[78110-38-0]	1984
imipenem ^{a,f}	[74431-23-5]	1985

^a Semisynthetic products.
^b First oral cephalosporins.
^c First commercial cephamycin.
^d First β-lactamase inhibitor combination.
^e First monobactam and a synthetic product.
^f First carbapenem.

Nomenclature

Antibiotics, and all other marketed drug products, are identified by three different types of names: (1) a chemical name based on standard rules of chemical nomenclature, (2) a generic (nonproprietary) name that is relatively short and follows a systematic procedure of describing a compound structure-type and utility, and (3) a trade name that is given by the manufacturer to distinguish it from competitive products. Some of the antibiotics discovered prior to 1961, when the U.S. adopted names (USAN) program started, had received many different names in the chemical literature. The USAN program is a specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drug is still in its investigational stage (10). Most of the antibiotics reported in literature are not of commercial interest and are not given generic names. If the chemical name is too complex, a trivial (nonsystematic or semisystematic) name is often assigned by the discoverer. For industrial organizations these names usually appear as alphanumeric coded identifiers such as LL-F28249α, given the generic name of nemadectin when the commercial potential became apparent (11).
A marketed antibiotic's generic name is usually preferred because it is simpler and easier to remember. Tetracycline [60-54-8], is an example:

chemical name	4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-napht hacenecarboxamide
generic name	tetracycline
trade names	Achromycin (Lederle), Panmycin (Upjohn) Sumycin (Squibb), Tetracyn (Pfizer), Tetrex (Bristol), etc

Classification of Antibiotics

Antibiotics have a wide diversity of chemical structures and range in molecular weight from near 100 to over 13,000. Most of the antibiotics fall into broad structure families. Because of the wide diversity and complexity of chemical structures, a chemical classification scheme for all antibiotics has been difficult. The most comprehensive scheme may be found in reference 12. Another method of classifying antibiotics is by mechanism of action (5). However, the modes of action of many antibiotics are still unknown and some have mixed modes of action. Usually within a structure family, the general mechanism of action is the same. For example, of the β-lactams having antibacterial activity, all appear to inhibit bacterial cell wall biosynthesis.

A chemical classification of some of the commercially more important antibiotic families that is generally consistent with the scheme of reference 12, is given here (2).

Aminoglycosides. Antibiotics in the aminoglycoside group characteristically contain amino sugars and deoxystreptamine or streptamine. This family of antibiotics has frequently been referred to as aminocyclitol aminoglycosides. Representative members are streptomycin, neomycin, kanamycin, gentamicin, tobramycin, and amikacin. These antibiotics all inhibit protein biosynthesis.

Ansamacrolides. Antibiotics in the ansamacrolide family are also referred to as ansamycins. They are benzenoid or naphthalenoid aromatic compounds in which nonadjacent positions are bridged by an aliphatic chain to form a cyclic structure. One of the aliphatic–aromatic junctions is always an amide bond. Rifampin is a semisynthetically derived member of this family and has clinical importance. It has selective antibacterial activity and inhibits RNA polymerase.

β-Lactams. All β-lactams are chemically characterized by having a β-lactam ring. Substructure groups are the penicillins, cephalosporins, carbapenems, monobactams, nocardicins, and clavulanic acid. Commercially this family is the most important group of antibiotics used to control bacterial infections. The β-lactams act by inhibition of bacterial cell wall biosynthesis.

Chloramphenicol. Only chloramphenicol and a few closely related analogues fall into this group. Chloramphenicol, a nitro benzene derivative of dichloroacetic acid, inhibits protein biosynthesis.

Glycopeptides. Vancomycin, avoparcin, and teicoplanin are examples of glycopeptide antibiotics. This family has cyclic peptide structures and biphenyl containing amino acids. Sugars are attached to the peptide unit resulting in compounds frequently in the molecular weight range of 1400–2000. These antibiotics inhibit bacterial cell wall biosynthesis by binding to D-alanyl-D-alanine units found in the cell walls.

Lincomycin. The lincomycins and celesticetins are a small family of antibiotics that have carbohydrate-type structures. Clindamycin, a chemical modification of lincomycin, is clinically superior. Antibiotics in this family inhibit gram-positive aerobic and anaerobic bacteria by interfering with protein biosynthesis.

Macrolides. Antibiotics in the macrolide group are macrocyclic lactones that can be further classified into two main subgroups: (1) polyene macrolides that are antifungal agents and include compounds like nystatin and amphotericin B; and (2) antibacterial antibiotics represented by erythromycin and tylosin. A number of other subfamilies of antibacterial and antifungal antibiotics fall into the broad category of macrolides.

Polyethers. Antibiotics within this family contain a number of cyclic ether and ketal units and have a carboxylic acid group. They form complexes with mono- and divalent cations that are soluble in nonpolar organic solvents. They interact with bacterial cell membranes and allow cations to pass through the membranes causing cell death. Because of this property they have been classified as ionophores. Monensin, lasalocid, and maduramicin are examples of polyethers that are used commercially as anticoccidial agents in poultry and as growth promotants in ruminants.

Tetracyclines. The tetracyclines are a small group of antibiotics characterized as containing a polyhydronaphthacene nucleus. Commercially the tetracyclines are very important. They have been used clinically against gram-positive and gram-negative bacteria, spirochete, mycoplasmas, and rickettsiae

and have veterinary applications in promoting growth and feed efficiency. The mode of action is inhibition of protein synthesis. Some of the more important members of this family are tetracycline, minocycline, and doxycycline.

Production

Most of the microorganisms used to produce antibiotics were isolated from soil samples. These microorganisms occur as heterogenous populations and generally inhabit the top few centimeters of soil. Families demonstrated to produce antibiotics include actinomycetes , bacteria, and fungi. Actinomycetes are in numbers the most productive for antibiotics. Until 1974 antibiotics produced by actinomycetes were almost exclusively from the genus *Streptomyces*, accounting for 95° of the total of about 2000 antibiotics known at that time. Thereafter, the role of "rare" actinomycetes as an antibiotic source became apparent as these latter organisms provided about 25° of the approximately 1100 antibiotics from actinomycete origin discovered in the next six years. The rare actinomycetes include genera such as *Actinoplanes*, *Micromonospora*, and *Nocardia*. Their capacity to produce diverse antibiotic structures is comparable to *Streptomyces*; however, the isolation of these organisms is less frequent by conventional isolation techniques (13).

To obtain reproducible antibiotic production by fermentation, it is necessary to obtain a pure culture of the producing organism. Pure cultures are isolated from mixed soil sample populations by various streaking and isolation techniques on nutrient media. Once a pure culture has been found that produces a new antibiotic typically on a mg L scale, improvement in antibiotic yield is accomplished by modification of the fermentation medium or strain selection and mutation of the producing organism. Production of g L quantities may take years to accomplish.

The vast majority of new antibiotics result from screening soil microorganisms or by semisynthetic modification of naturally occurring antibiotics. One alternative approach, termed directed biosynthesis, involves feeding potential biosynthetic precursors into a fermentation of a known antibiotic in order to produce new components (13,14). This approach was used in the early development stages of the penicillins to obtain penicillin G. Phenylacetic acid was fed to fermentations of *Penicillium chrysogenum*. Another approach involves bioconversions. A known antibiotic is added to the fermentation of a microorganism that is capable of carrying out a process such as hydroxylation or amination. Modifications of these types can frequently be accomplished with a selectivity that is difficult to obtain by synthetic methods. A procedure called mutasynthesis, first reported with regard to new antibiotics related to neomycin (15,16), is sometimes used.

Genetic engineering (qv) technology has evolved that allows modifications of the microorganisms' DNA to produce new material. The structure of indolizomycin, the first new antibiotic obtained by a procedure known as protoplast fusion (17), was totally different from the antibiotics produced by the grandparental strains of *Streptomyces griseus* and *S. tenjimariensis* used in the fusion experiment. Cloning of genes involved in antibiotic biosynthesis from actinomycetes has become possible. The generation of the mederthodin A producing *Streptomyces* clone was the first example of antibiotic production using *in vitro* recombinations (18). Gene segments from *S. coelicolor*, the producer of actinothodin, were introduced into *Streptomyces* sp. AM7161, the producer of a related antibiotic called medernmycin. Through this manipulation a clone producing a new medernmycin derivative was obtained.

Commercial fermentations are conducted in large bioreactors which are usually referred to as fermentors and are designed for operation in batch, fed-batch, or continuous fermentation (qv) modes (19). The organism is grown at constant temperature in a sterile nutrient medium, containing a carbon source, a nitrogen source, and a small amount of inorganic salts, under controlled conditions of aeration (qv) and agitation. The media for commercial fermentations are usually complex mixtures containing relatively inexpensive nutrients such as molasses , corn steep liquor, or soy meal. A batch fermentation is a closed system containing sterilized medium inoculated with the desired microorganism. Incubation is allowed to proceed under optimal physiological conditions and nothing is added during the course of the fermentation except oxygen, an antifoam agent (see DEFOAMERS), and acid or base to control the pH. In the fed-batch process, nutrients are added in increments as the fermentation progresses. In the continuous fermentation, nutrient solution is added to the bioreactor continuously as an equivalent volume of converted nutrient solution with microorganisms is simultaneously removed from the system for processing.

The batch and fed-batch procedures are used for most commercial antibiotic fermentations. A typical batch fermentor may hold over 150,000 liters. When a maximum yield of antibiotic is obtained, the fermentation broth is processed by purification procedures tailored for the specific antibiotic being produced. Nonpolar antibiotics are usually purified by solvent extraction procedures; water-soluble compounds are commonly purified by ion-exchange methods. Chromatography procedures can readily provide high quality material, but for economic reasons chromatography steps are avoided if possible.

Most of the new commercial antibiotics have resulted from semisynthetic studies. New cephalosporins, a number of which are synthesized by acylation of fermentation-derived 7-aminocephalosporanic acid, are an example. Two orally active cephalosporins called cefroxadine and cephalixin are produced by a synthetic ring-expansion of penicillin V.

Economic Aspects

The world antibiotic market for 1989, estimated at 12.3 billion dollars (20), was the second biggest pharmaceutical category accounting for approximately 9° of the total world pharmaceutical market. Cardiovascular agents (qv) were first. In 1988 antibiotic production in the United States was 13.1 × 10⁶ kg compared to central nervous system depressants and stimulants, 22.3 × 10⁶ kg, gastrointestinal agents and therapeutic nutrients, 45.2 × 10⁶ kg, and vitamins, 17.5 × 10⁶ kg (21). The leading pharmaceutical companies for the manufacture and sales of antibiotics in 1989 are listed in Table 2 (2).

Table 2. Antibiotic Pharmaceutical Manufacturers for 1989

Company	Market share, ° a
Eli Lilly	11.5
Smith Kline Beecham	9.3
Bristol-Myers Squibb	8.6
Shionogi	7.0
Hoffmann-La Roche	6.9
Pfizer	6.4
Merck	6.4
Hoechst	6.3
Takeda	5.1
Fujisawa	4.7
others	27.8

a 1989 world market estimated at \$12.3 × 10⁹ (20).

Japan held 37.5° of the world antibiotic market in 1988, the USA 23.2° , Italy 8.0° , the United Kingdom 5.4° , Germany 3.6° , and other countries 22.3° (20). The disproportionate size of the Japanese market is in part a consequence of the inherent strengths of Japanese industry which include expertise in fermentation technology and intensive chemical manipulation of known structures. In addition, antibiotic prescribing in Japan is extremely popular among doctors as a result of the Japanese reimbursement system.

Uses

Antibacterial Agents. There is a continuous need for new antibiotics primarily as a result of bacterial resistance. There are two aspects to this phenomenon. First, as the more common pathogens are controlled by antibiotics, less common, highly resistant organisms present more prominent health

problems. Examples are infections resulting from *Pseudomonas* and *Enterobacter*. Second, and this has been the major driving force in the antibiotic market, particularly in the hospital sector, there is emerging resistance. This type of bacterial resistance can take place through one or more mechanisms including reduced target affinity, target bypass, drug inactivation, reduced permeability of bacterial cells, and drug efflux from the organism. Resistance can be passed from one organism to another through plasmids which are highly mobile segments of bacterial DNA. This transfer of resistance can even occur between different species and genera of bacteria.

The development of new antibiotics to combat resistance, and to provide easier oral administration and improved pharmacokinetics has been successful through synthetic modifications. This approach has been particularly rewarding in the area of β -lactams. The commercial importance of the β -lactams is evident from Table 3 which gives the market share of antibacterials. Fully 62% of the 1989 world antibacterial market belonged to the cephalosporin and penicillin β -lactams (20).

Table 3. 1989 World Antibacterial and Antibiotic Market

Structural classification	Market share, % ^a
cephalosporins	48
penicillins	14
quinolones (synthetic)	11
macrolides	8
aminoglycosides	6
tetracyclines	6
others	7

^a 1989 world market estimated at \$12.3 $\times$ 10⁹ (20).

Anticancer Agents. In the latter 1980s antibiotics became more important in the treatment of cancer (see CHEMOTHERAPEUTICS, ANTICANCER). In 1987 the antitumor antibiotic adriamycin [23214-92-84] was one of the top 50 drugs worldwide. Its revenues were estimated at \$231 million (22). Other important antibiotics clinically used for treatment of cancer include bleomycin [11056-06-7] and mitomycin C [50-07-7]. These compounds are all toxic both to bacteria and to mammalian cells because they interact with DNA. Although antibiotics of this type are not useful as antibacterial agents because of their toxicity and resulting low safety margins, they are useful as antitumor agents. They do show some selective toxicity to rapidly proliferating cancer cells.

Antituberculin Agents. Rifampin [13292-46-1], a semisynthetic derivative of rifamycin SV, is a most valuable drug for treatment of tuberculosis, an infection caused by mycobacteria, leprosy, and an expanding range of other infections (23). Cycloserine [64-41-7] has been used to a limited extent for treatment of tuberculosis as a reserve drug. Although cycloserine inhibits bacteria by interfering with their cell wall biosynthesis, it has toxic side effects in humans in the form of neurotoxicity. Capreomycin [11003-38-6] and to a much lesser extent viomycin [32988-50-4], both of which are peptides, have also been used for treatment of this disease.

Antifungal Agents. Antibiotics have been effective in the treatment of fungal diseases (see ANTIPARASITIC AGENTS, ANTIMYCOTICS). Because these types of infections are less prevalent than bacterial infections, the market for antifungal antibiotics has been relatively small. In 1989 the total world market for systemic antifungal agents was \$290 million and antifungal antibiotics accounted for approximately 4% (24). However, as the number of immunocompromised patients increases as a result of therapy following organ transplants, acquired immunodeficiency syndrome (AIDS), and anticancer chemotherapy, the need for new and improved antifungal agents may increase significantly. Amphotericin B [1397-89-3], a polyene antibiotic, remains the most useful drug for systemic treatment of serious fungal infections despite its inherent toxicity (23). Other clinically used antifungal polyene antibiotics include nystatin and pimaricin [7681-93-8], however, applications are essentially limited to superficial infections. They are too toxic for parenteral administration. Griseofulvin [126-07-8], which has a structure containing a spiro ring system, is a very good drug for treatment of dermatophyte or ringworm infections.

Antiviral Agents. Although a number of antibiotics have been shown to have some sort of antiviral activity, only vidarabine [5536-17-4] (adenine arabinoside) is used clinically against viral infections at this time. As the need for new antiviral agents (qv) increases and new screening procedures are developed, one would expect the discovery of other new effective antiviral antibiotics that could be used safely in human therapy.

Veterinary Applications. Another use for antibiotics is for veterinary applications and for animal feed supplements to promote growth in livestock (see FEEDS AND FEED ADDITIVES). Feed antibiotics used in the United States far surpass all other agricultural applications in terms of kilogram quantities used and approach quantities used in human medicines (25). In 1980 the USA feed antibiotic usage was estimated to be between five and six million kg. The U.S. Council of Agricultural Science and Technology estimates that feed additives save the U.S. consumer approximately \$3500 million per year in meat prices, and antibiotic use accounts for most of this.

Feed additive antibiotics achieved sales estimated at \$710 million in 1989. This market was dominated by tetracyclines and tylosin [1401-69-0] which are believed to account for over 50% of antibiotic sales for this use (26). Other important feed antibiotics include bacitracin, virginiamycin [11006-76-1], bambarmycin [11015-37-5], lincomycin, and spiramycin [8025-81-8]. The growth promoting effect of most of these antibiotics is believed to result from subtherapeutic treatment of diseases. In addition, there is another group of antibiotics that effect growth rate and feed efficiency in livestock in the absence of disease. Key products in this area include the polyether ionophores monensin [17090-79-8] and lasalocid [25999-31-9] and the glycopeptide avoparcin [37332-99-3]. In 1989 the total estimated world market sales for these types of growth promoters was \$132 million (see GROWTH REGULATORS).

Coccidiosis is a protozoal disease of the intestinal tract of animals that leads to severe loss of productivity and death. The development and widespread use of anticoccidials has revolutionized the poultry industry. The estimated world market for anticoccidial agents in 1989 was \$425 million and this was dominated by the polyether ionophore antibiotics monensin, salinomycin [53003-10-4], narasin [55134-13-9], lasalocid, and maduramicin [84878-61-5] (26).

Antimicrobials, a diverse group of products including antibiotics for therapeutic treatment, had estimated worldwide sales of \$1500 million in 1989, excluding feed applications, and represent the largest sector in the animal pharmaceutical area. The tetracycline antibiotics represent the largest part of this group having an estimated \$475 million in sales. The penicillins with \$110 million and macrolides with \$250 million in sales in 1989 also represent large segments of this market (26).

Another very important agricultural application for antibiotics is in the area of anthelmintics (see ANTIPARASITIC AGENTS, ANTHELMINTICS). The anthelmintic area is the second largest veterinary pharmaceutical market worldwide. The worldwide anthelmintic market in 1988 was estimated to be \$850 million. The largest selling single anthelmintic agent was ivermectin [30288-86-7], which had estimated sales of \$245 million (26) (see ANTIPARASITIC AGENTS, AVERMECTINS).

Ivermectin is the catalytic reduction product of avermectin, a macrolide containing a spiroketal ring system. Two other related antibiotics having significantly different structural features and biological properties, moxidectin and milbemycin oxime, were more recently introduced into the market. Although these compounds have no antimicrobial activity, they are sometimes referred to as antibiotics because they are derived from fermentation products and have very selective toxicities. They have potent activity against worms or helminths and certain ectoparasites such as mites and ticks.

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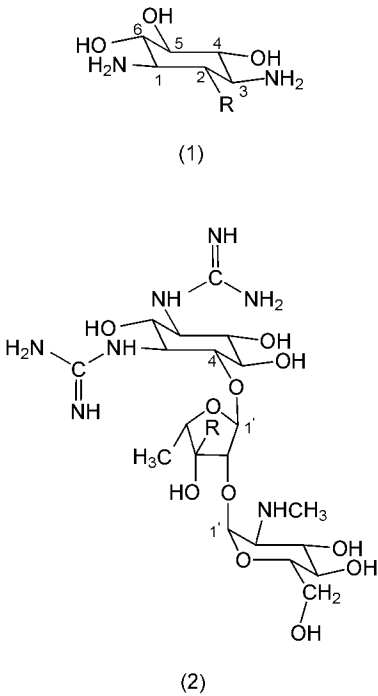
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AMINOGLYCOSIDES

The term *aminoglycoside* is commonly used to refer to members of the class of antibacterial antibiotics, the structures of which are derived from D-streptamine [488-52-8] C₁₄H₁₄N₂O₄ (1, R = OH), D-2-deoxystreptamine [2037-48-1] C₁₄H₁₄N₂O₃ (1, R = H), or closely related compounds. The terms *aminocyclitol* and *aminoglycoside-aminocyclitol* are also sometimes used to identify this group of compounds.

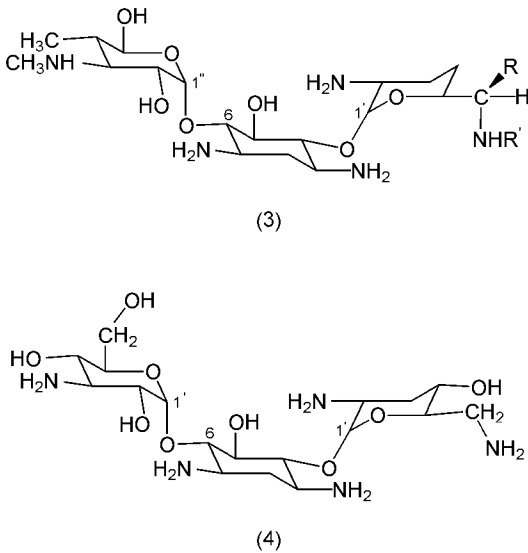


Historically, the first example of an aminoglycoside antibiotic is generally considered to be streptomycin [57-92-1] C₂H₃₉N₇O₁₂ (2, R = CHO), or streptomycin sulfate [3810-74-0] (chemical name: O-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N,N'-bis(aminoiminomethyl)-L-streptamine) isolated in 1944 from a strain of *Streptomyces griseus* (1–4). This discovery, a milestone in the history of antibacterial chemotherapy (5), was the starting point for research and development activities that continue to be important in the management of bacterial infectious disease.

Aminoglycosides in Medical Usage

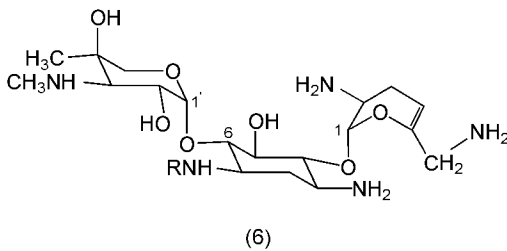
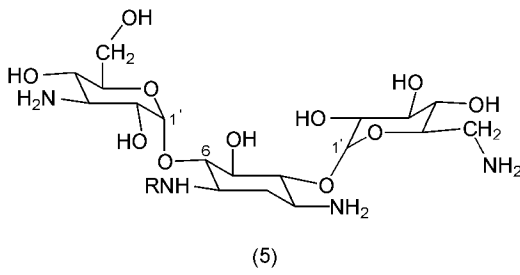
In 1991 the following aminoglycosides were most important in medical practice. Clinical experience is most extensive for the first four.

(1) Gentamicin [1403-66-3] or gentamicin sulfate [1405-41-0], is a mixture of gentamicin C₁ [25876-10-2] C₂₁H₄₃N₅O₇ (3, R = R' = CH₃), gentamicin C₂ [25876-11-3] C₂₀H₄₁N₅O₇ (3, R = CH₃, R' = H), and gentamicin C_{1a} [26098-04-4] C₁₉H₃₉N₅O₇ (3, R = R' = H) isolated from *Micromonospora purpurea* and related species (6–9). Note that compounds obtained from *Micromonospora* species are given names ending in -micin; those isolated from *Streptomyces* end in -mycin. The chemical name for gentamicin C_{1a} is O-3-deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)-O-[2,6-diamino-2,3,4,6-tetra-deoxy-α-D-erthrya-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine.

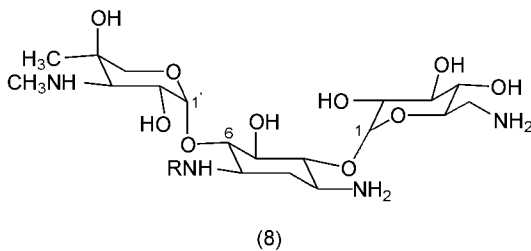
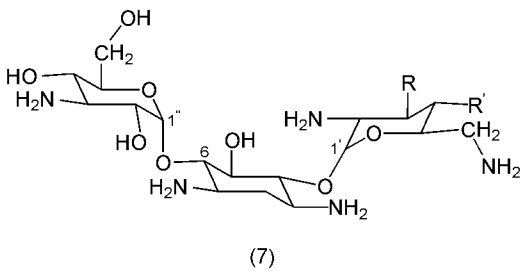


(2) Tobramycin [32986-56-4] C₁₈H₃₇N₅O₉, or tobramycin sulfate [79645-27-5], also called nebramycin factor 6, (4) (10–16), was isolated from *Streptomyces tenebrarius* and has the chemical name

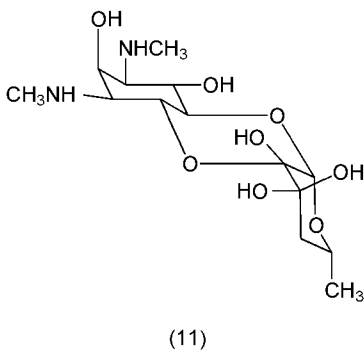
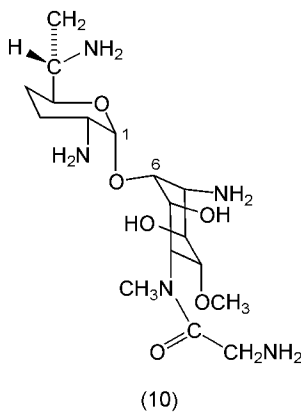
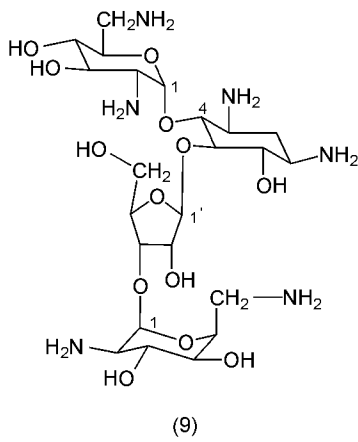
O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 6)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl-(1 $\rightarrow$ 4)]-2-deoxy-D-streptamine.
(3) Amikacin [37517-28-5] C₂₂H₄₃N₅O₁₃, or amikacin sulfate [39831-55-5] (5, R = (*S*)-COCHOHCH₂CH₂NH₂) is a semisynthetic derivative (17) of kanamycin A [59-01-8] C₁₈H₃₇N₅O₁₁ (5, R = H) which is produced by *Streptomyces kanamyceticus* (18–22). Amikacin has the chemical name (*S*)-*O*-3-amino-3-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 6)-*O*-[6-amino-6-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-*N*¹-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-D-streptamine.



(4) Netilmicin [56391-56-1] C₂₁H₄₁N₅O₇, or netilmicin sulfate [56391-57-2], (6, R = CH₂CH₃) is a semisynthetic derivative (23) of sisomicin [32385-11-8] C₁₉H₃₇N₅O₇, (6, R = H). Sisomicin is produced by *Micromonospora inyoensis* (24–26). Netilmicin has the chemical name *O*-3-deoxy-4-*C*-methyl-3-(methylamino)- β -L-arabinopyranosyl-(1 $\rightarrow$ 6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy- α -D-*glycem*-hex-4-enopyranosyl-(1 $\rightarrow$ 4)]-2-deoxy-*N*¹-ethyl-D-streptamine.
(5) Dibekacin [34493-98-6], C₁₈H₃₇N₅O₈, (7, R = R' = H), chemical name *O*-3-amino-3-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy- α -D-*erythm*-hexopyranosyl-(1 $\rightarrow$ 4)]-2-deoxy-D-streptamine, is a semisynthetic derivative (27,28) of kanamycin B [4696-78-8] C₁₈H₃₇N₅O₁₀ (7, R = R' = OH)
(*O*-3-amino-3-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 6)-*O*-[2,6-diamino-2,6-dideoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]-2-deoxy-D-streptamine) (29,30).



(6) Isepamicin [58152-03-7], C₂₂H₄₃N₅O₁₂, (8, R = (*S*)-COCHOHCH₂NH₂)
(*S*)-*O*-6-amino-6-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)- β -L-arabinopyranosyl-(1 $\rightarrow$ 6)]-*N*¹-(3-amino-2-hydroxy-1-oxopropyl)-2-deoxy-D-streptamine, which was introduced in 1988, is a semisynthetic derivative (31) of gentamicin B [36889-15-3] C₁₉H₃₈N₄O₁₀ (8, R = H) (32).
(7) Neomycin [1404-04-1] (33) or neomycin sulfate [1405-10-3], isolated from *Streptomyces fradiae* (34–36), is sometimes used for gut sterilization and other nonsystemic applications. Neomycin is a mixture of neomycin B [119-04-0] C₂₃H₄₄N₄O₁₃ (9)
(*O*-2,6-diamino-2,6-dideoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-*O*-[*O*-2,6-diamino-2,6-dideoxy- β -L-idopyranosyl-(1 $\rightarrow$ 3)- β -D-ribofuranosyl-(1 $\rightarrow$ 5)]-2-deoxy-D-streptamine) and neomycin C [66-86-4] C₂₃H₄₄N₄O₁₃. Neomycin C is 5'''-epi-neomycin B. Neomycin B is the main component.



- (8) Astromicin [55779-06-1], C₁₇H₃₅N₅O₇, (10)
(4-amino-1-[(aminoacetyl)methylamino]-1,4-dideoxy-3-O-(2,6-diamino-2,3,4,6,7-pentadeoxy-β-L-*xyxo*-heptopyranosyl)-6-O-methyl-L-*chiro*-inositol), also known as fortimicin A, is a member of a complex isolated from *Micromonospora olivoasterospora* (37–40). Although astromicin has a structure that is considerably different from those of the other aminoglycosides listed in this section, it is still an aminocyclitol joined to an aminosugar via a glycosidic linkage. Astromicin was introduced in limited markets in 1987.
- (9) Spectinomycin [21736-83-4], C₁₄H₂₄N₂O₇, or spectinomycin pentahydrate [22189-32-8] (11)
(decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methyl-amino)-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one) is not strictly an aminoglycoside, but its structure does contain a modified streptamine moiety. The ketone group on position 4 exists as the hydrate. Spectinomycin was isolated from *Streptomyces spectabilis* (41–43). Although it has a fairly broad antibacterial spectrum, medical usage is confined to the treatment of *Neisseria gonorrhoea* infections and it is the agent of choice for resistant strains of that species.

Among the older aminoglycoside derivatives, kanamycin A and sisomicin were, at one time, a significant part of medical practice, but have now been largely replaced by the compounds listed in Table 1. Streptomycin is still used in a few restricted situations.

Table 1. Annual Worldwide Estimated Sales of Aminoglycosides

Aminoglycoside			Annual worldwide estimated sales, U.S.\$ × 10 ⁶		
Generic name	Trade name	Company	1988	1989	1990
gentamicin	Garamycin and others ^a	Schering-Plough and others ^a	120	130	140
tobramycin	Nebcin	Lilly	170	150	150
amikacin	Amikin	Bristol-Myers Squibb	190	190	200
netilmicin	Netromycin	Schering-Plough	130	130	130
dibekacin	Panimycin	Meiji Seika	60	50	50
isepamicin	Isepacin	Schering-Plough	20	45	45
	Exacin	Toyo Jozo			
Other aminoglycosides			120	95	85
Total			810	790	800

^a Gentamicin is off patent, and is currently marketed by several companies.

Medical and Biological Properties

General Antibacterial Properties. In the clinical control of bacterial infectious disease, the aminoglycosides gentamicin, tobramycin, amikacin, netilmicin, and to a lesser extent, dibekacin and isepamicin are most commonly used for the treatment of serious infections involving aerobic or facultative gram-negative bacilli, especially in the compromised host. This usage is discussed in the literature (44–51).

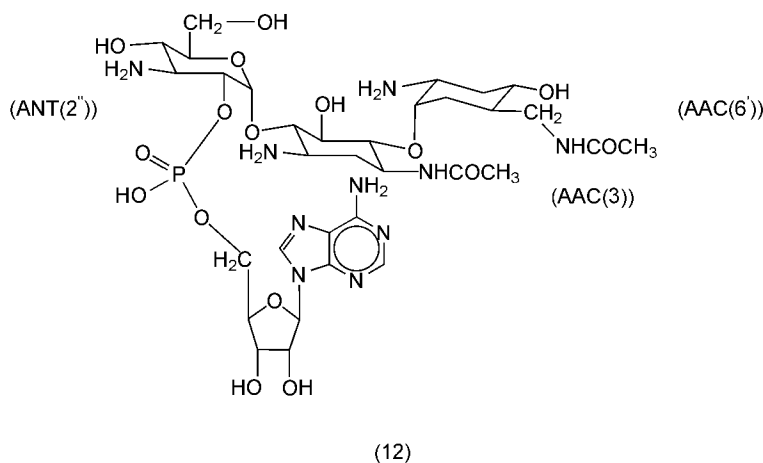
Overall, these aminoglycosides are approximately equally effective for the clinical treatment of infections involving susceptible strains of *Escherichia coli*, *Klebsiella sp.*, *Enterobacter sp.*, *Citrobacter sp.*, *Serratia sp.*, *Proteus mirabilis*, *Morganella morganii*, *Proteus vulgaris*, *Proteus rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, and the gram-positive species *Staphylococcus aureus*. Other gram-positive bacteria, such as *Streptococcus sp.*, and anaerobes are not generally susceptible to aminoglycosides (52–56). There are some differences in the *in vitro* activities of the various aminoglycosides against these species. Tobramycin (4) tends to have better *in vitro* activity against *P. aeruginosa* than gentamicin (3), but it has been difficult to show that these differences are reflected in clinical performance. There are also differences in potency. Amikacin (5, R = (S)-COCHOHCH₂CH₂NH₂), for example, is generally less potent than the others, but a decreased toxicity allows the dose to be adjusted for comparable efficacy. Thus, especially in the case of the four aminoglycosides for which there is the greatest amount of clinical experience, ie, gentamicin, tobramycin, amikacin, and netilmicin (6, R = CH₂CH₃), there does not appear to be a significant difference in the outcome of treatment of infections (57) due to sensitive strains of these bacteria.

Particular advantages of the aminoglycosides are that, in general, the bactericidal concentration is not significantly different from the growth inhibitory concentration and, furthermore, the bactericidal effect is rapid and concentration dependent (58). In very serious infections such as occur in febrile neutropenic patients or in enterococcal endocarditis, a combination of an aminoglycoside with a β-lactam antibiotic (see ANTIBIOTICS, β-LACTAMS) or vancomycin (see ANTIBIOTICS, GLYCOPEPTIDES) is often used. In addition to extending the spectrum of coverage, such combinations are often found to be synergistic. They have a greater inhibitory effect than would be predicted from additivity alone (59–61). However, under sufficiently concentrated conditions, β-lactams and aminoglycosides can inactivate each other by acylation of one of the amino groups (62).

Bacterial Resistance Mechanisms. The occurrence of antibiotic resistant bacterial strains is an important medical problem. This is especially true for nosocomial infections (63–65). The incidence and type of resistance are highly variable phenomena that can change with time and location. In some cases, these strains can arise in response to the environmental pressure of aminoglycoside usage. However, the incidence of aminoglycoside resistance overall has remained relatively stable throughout the 1980s and into the 1990s (51). Of the aminoglycosides in current use, amikacin and isepamicin (8, R = (S)-COCHOHCH₂NH₂) are least susceptible to the bacterial resistance mechanisms, netilmicin and dibekacin (7, R = R' = H) are intermediate, and gentamicin and tobramycin are most susceptible (66). Resistance to streptomycin is widespread, and its use is currently confined primarily to infections caused by *Mycobacterium tuberculosis*, *Yersinia pestis*, and *Francisella tularensis*.

Resistance to the antibacterial action of aminoglycosides is mediated primarily by three mechanisms: (1) Changes in the bacterial ribosome such that the affinity for the antibiotic is significantly decreased. This mechanism appears to be relatively rare except for streptomycin (67). (2) Significant reduction in the rate at which the aminoglycoside passes through the cell wall and cell membrane into the cytoplasm. This phenomenon is presumably responsible for the intrinsic resistance of *Streptococcus sp.* and anaerobic bacteria to the action of aminoglycosides. It may also be an important component of acquired resistance (68). (3) Inactivation of the aminoglycoside by plasmid-borne enzymes which catalyze acetylation, phosphorylation, or adenylation reactions. This is the most common of the resistance mechanisms, and is a significant clinical problem. A large number of aminoglycoside acetyltransferase (AAC), aminoglycoside phosphotransferase (APH), and aminoglycoside nucleotidyltransferase (ANT), also referred to as aminoglycoside adenylyltransferase (AAD), enzymes and related isozymes have been found. These enzymes differ in the substrates on which they operate, their catalytic efficiency, and in the product produced (68–73).

The most clinically significant of the aminoglycoside inactivating enzymes seem to be (74): ANT(2''), an enzyme that catalyzes the transfer of an adenylyl group to the 2''-hydroxy of gentamicin, tobramycin, dibekacin, and kanamycins A and B; AAC(6')-(various isozymes), enzymes that catalyze the transfer of an acetyl group to the 6'-amino of gentamicin, tobramycin, amikacin, isepamicin, netilmicin, kanamycins A and B, sisomicin, dibekacin, and neomycin; and AAC(3)-(various isozymes), enzymes that catalyze the acetylation of the 3-amino moiety of gentamicin, tobramycin, netilmicin, kanamycins A and B, dibekacin, neomycin, and astromicin. If all three of these enzymes were to operate on tobramycin (4), the result would be structure (12) (20).



Other enzymes that may play a role clinically are AAC(2'), important in some *Providencia* and *Proteus* species, APH(3'), and APH(3'') (71). Others that have been observed include APH(2''), APH(5''), APH(6), ANT(4'), ANT(3''), and ANT(6). It has been suggested that, for effective resistance, an organism must have both impaired aminoglycoside transport and levels of aminoglycoside inactivating enzymes such that the rate of inactivation in the cytoplasm is greater than the rate of influx (68).

Pharmacokinetics. The aminoglycosides are not reliably absorbed following oral dosing, so they are administered primarily by intravenous infusion or intramuscular injection (75–77). Distribution throughout the vascular and interstitial space occurs fairly rapidly. Because these antibiotics are polycationic and relatively large, biological membranes are not readily crossed, unless transport mechanisms exist as in the kidney proximal tubule cells, and intracellular levels are generally low. Levels in the cerebrospinal fluid (CSF), bronchial secretions, and saliva are also low. Aminoglycoside excretion takes place almost entirely via the kidneys. Most of the compound is eliminated unmetabolized in a relatively rapid beta phase having a half-life of 2–3 h. A small portion, however, is excreted in a slow gamma phase, half-life 35–200 h. Because of the relatively short beta-phase half-life, dosing is usually two or three times per day. Efficient clearance is dependent on glomerular function and, when glomerular filtration rate is reduced because of age or kidney disease, particular care in dosing must be exercised to prevent accumulation of toxic aminoglycoside levels (78). Some studies have shown that, for certain clinical applications, an aminoglycoside can be administered once a day and efficacy is unchanged while toxicity is decreased (79–82). A possible contributor to the success of this strategy is the observation of a post-antibiotic effect (83), in which growth inhibition of some bacterial species continues for a period of time after the serum concentration of the aminoglycoside drops below the presumed inhibitory level.

A novel approach to the modification of aminoglycoside pharmacokinetics is under investigation (84). Administration of gentamicin encapsulated in egg phosphatidylcholine liposomes has been found to lead to a longer half-life and much higher spleen and liver levels for the gentamicin component. This formulation is undergoing clinical study (85).

Toxicology. A primary limiting factor in the clinical use of the aminoglycosides is the potential toxicity. This toxicity prevents the use of significantly increased doses to cover difficult infections. Also, serum aminoglycoside concentrations can reach toxic levels even when normal doses are used because of variation in glomerular filtration efficiency. All the aminoglycosides in medical practice are capable of causing these adverse reactions

(51,57,77,86).

The principal aminoglycoside toxicities are neuromuscular paralysis, ototoxicity, and nephrotoxicity. Neuromuscular paralysis is a relatively rare complication resulting from high aminoglycoside concentrations at the neuromuscular junctions following, for example, rapid bolus intravenous injection or peritoneal instillation, rather than the normal intravenous infusion. The mechanism apparently involves an inhibition of both the presynaptic release of acetylcholine and the acetylcholine postsynaptic receptors (51).

Both auditory (cochlear) (high frequency hearing loss), and vestibular (nausea, vertigo) dysfunctions are experienced (87). Whereas the ototoxic responses are not life-threatening, these effects are especially significant because they are often irreversible and cumulative. The incidence is estimated at from 0.5 to 25%. The wide range is partially a reflection of the difficulty in measuring this kind of toxic effect (51). The mechanisms involved in these reactions are not fully understood, but they apparently involve damage to hair cells in the organ of Corti and ampullar cristae, neither of which can regenerate. All of the commonly used aminoglycosides can cause both cochlear and vestibular effects, but amikacin is more likely to cause the cochlear type of toxicity (88,89) and particularly severe auditory dysfunction has led to the restriction of neomycin use to topical applications. Overall, however, the incidence of clinical ototoxicity seems to be comparable for each of the different aminoglycosides (51,57), with the possible exception of a reduced incidence for netilmicin (86,89,90). In a comparative study using a guinea pig model, the increasing order of cochlear toxicity was found to be netilmicin, dibekacin, amikacin, tobramycin, gentamicin; the order of vestibular toxicity was amikacin, netilmicin, tobramycin, dibekacin, gentamicin (90).

Estimates of the incidence of nephrotoxicity range from 5 to 25%. In most cases, the observed effects are a mild-to-moderate decrease in glomerular filtration rate accompanied by the urinary excretion of renal tubular enzymes. The effects are usually reversible, and their likelihood is reduced by monitoring serum levels and glomerular filtration rate and adjusting the dosing accordingly. However, the possibility of a serious reaction, particularly in the compromised patient, represents a significant deterrent to aminoglycoside usage. It has been estimated that nephrotoxic reactions add an average of \$183 in hospital costs for each patient who receives an aminoglycoside (91). Overall, gentamicin and tobramycin may be somewhat more likely to be nephrotoxic than amikacin and netilmicin (51,89), but the differences are generally not significant (92). Preliminary experimental evidence in animal models indicate that isepamicin may be less nephrotoxic (93,94), but clinical evidence is not yet available. Spectinomycin does not have the nephrotoxic and ototoxic liabilities of the aminoglycosides nor does it have the breadth of antibacterial spectrum typical of the aminoglycosides.

Significant progress has been made in recent years toward understanding the mechanisms involved in the nephrotoxic effects of the aminoglycosides (52,77). The scheme which has evolved can be outlined as follows: (1) aminoglycoside in the serum is filtered through the glomerulus into the lumen of the kidney tubule; (2) an initial charge-mediated binding of the aminoglycoside to the brush border membrane of the kidney proximal tubule cells is followed by a pinocytotic uptake into those cells, possibly utilizing the basic amino acid transport system (95); (3) after uptake, the pinocytotic vesicles fuse with preexisting lysosomes, leading to a rapid and substantial accumulation of aminoglycoside in the lysosomes (96); (4) in the lysosome, the aminoglycoside appears to inhibit phospholipases, resulting in the accumulation of phospholipids in the form of myeloid bodies (phosphlipidosis) (97,98). Extralysosomal effects are also observed, particularly with respect to mitochondrial function (99–101); (5) in a step the mechanism of which is unclear, phospholipidosis and the other effects are followed by cell necrosis, then regeneration (102). This may involve destabilization of the lysosomal membrane or interference with membrane recycling processes. The extent of kidney damage can be viewed as a result of competitive rates of cell necrosis and regeneration (97).

A novel approach to the problem of aminoglycoside nephrotoxicity has been to search for compounds that can inhibit toxicity without compromising efficacy. A number of agents have been reported to reduce aminoglycoside toxicity in animal models; the most extensively studied of these is sodium polyaspartate (103–107).

Mechanism of Antibacterial Action. In spite of the fact that the antibacterial activity of the aminoglycosides has been known since the 1940s, the mechanisms involved are still incompletely understood. Numerous reviews have appeared (eg, 108–113) and the sequence of events seems to be as outlined below.

First, the cationic aminoglycoside binds to anionic groups on the bacterial cell surface. This step is both energy-independent and nonspecific. Then, the molecule passes through the cell wall via porins or self-promoted defects in the wall, traverses the periplasmic space, and arrives at the cell membrane. The next step has been termed the energy-dependent phase I and can be inhibited by compounds that block electron transport. According to one model, the aminoglycoside binds to a transporter molecule and, once a threshold electrical potential is reached, is translocated into the cytoplasm with the involvement of the electron-transport chain. Uptake, to the extent that it occurs during this phase, is small. In the energy-dependent phase II, there is an accelerated and irreversible aminoglycoside uptake into the cytoplasm. This step can be inhibited by inhibitors of both electron transport and protein synthesis, and is dependent on an interaction of the aminoglycoside with the ribosomes. One of the several suggested models for this step envisages a cell membrane that becomes increasing leaky because of the incorporation of faulty proteins resulting from aminoglycoside-induced errors in translation (114,115). In the cytoplasm, the aminoglycoside binds to the ribosome leading to a misreading of the genetic code (116), and the consequent production of abnormal proteins, and, at higher concentrations, an inhibition of protein synthesis. Cell death, the cause of which is uncertain, follows.

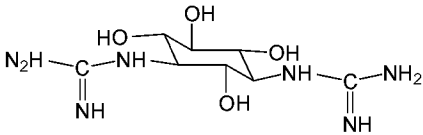
Aminoglycoside Biosynthesis. The biosynthesis of the aminoglycosides has been extensively studied and reviewed (117–119). Perhaps the most interesting aspect is the biosynthesis of 2-deoxystreptamine (1, R = H), in which the C-1 and C-6 of a D-glucose molecule become the C-1 and C-2 of 2-deoxystreptamine by way of the intermediate 2-deoxy-*scyllo*-inosose. The details of this conversion are still unclear.

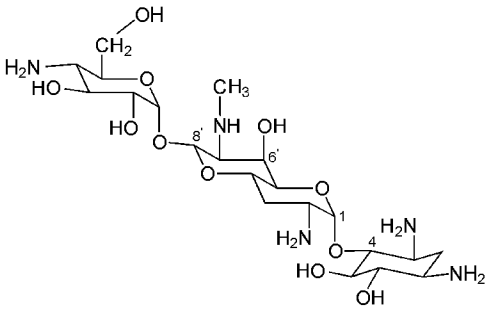
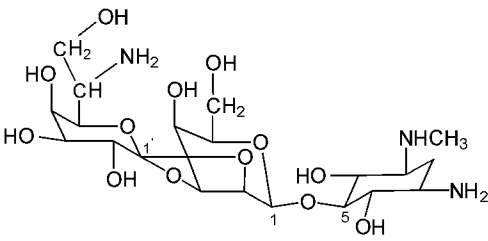
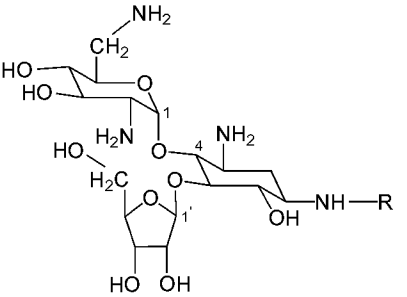
Structure-Activity Relationships Among Aminoglycoside Derivatives

The aminoglycosides possess properties that make them valuable for the control of bacterial infectious disease, but they also have distinct limitations, especially in the areas of toxicity and susceptibility to bacterial resistance mechanisms. Thus there has been a large amount of research aimed at reducing the limitations while maintaining the advantages generally by introducing modifications into the basic aminoglycoside molecular structure. In general, three approaches have been used to generate novel aminoglycoside structures. (1) Search for microorganisms that produce novel structures directly. This approach has resulted in gentamicin and tobramycin. (2) Chemically modify structures of molecules available from microorganisms ie, undertake semisynthesis. Netilmicin, amikacin, dibekacin, and isepamicin have resulted from this approach. (3) Generate microorganism mutants that require a modifiable exogenous substrate for the biosynthesis of the aminoglycoside. Because of the difficulty of the chemistry, total synthesis (120,121) has not yet been a major contributor of modified aminoglycosides.

The number of aminoglycoside derivatives reported over the years is very large. Much of the work has been summarized in reviews (120,122–125). Only the structural subclasses and representative derivatives are discussed here. Some of the structures are given in Table 2.

Table 2. Structures Relating to Aminoglycoside Derivatives

Name	CAS Registry Number	Molecular formula	Structure number	Structure
streptidine	[85-17-6]	C ₈ H ₁₈ N ₄ O ₄	(13)	
apramycin ^a	[37321-09-8]	C ₂₁ H ₄₁ N ₅ O ₁	(14)	

				
hygromycin B	[31282-04-9]	C ₂₀ H ₃₇ N ₃ O ₁	(15)	
				
ribostamycinb	[25546-65-0]	C ₁₇ H ₃₄ N ₄ O ₁	(16, R = H)(16, R =	
utirosin B	[34291-03-7]	C ₂₁ H ₄₁ N ₅ O	(S)-COCHOHCH ₂ CH ₂ NH	
				

^a Also known as nebramycin factor 2.

Derivatives of Streptidine. The first aminoglycoside to be isolated was streptomycin (2, R = CHO), which is a derivative of streptidine (13) shown in Table 2. A number of derivatives have been prepared (126), the most interesting of which was dihydrostreptomycin [12846-1/ C₂₁H₄₁N₇O₁₂ (2, R = CH₂OH), which retained the antimicrobial spectrum of its precursor. This derivative was removed from clinical usage because of a high incidence of ototoxicity. Even minimal modification of the guanidine groups in dihydrostreptomycin led to loss of activity, although a single methyl on the 1-guanidino was tolerated (127). The 3''-deoxy- and 3''-epidihydrostreptomycin derivatives were quite active and resistant to some inactivating reactions (128).

Derivatives Containing a 4-Monosubstituted-2-deoxystreptamine Moiety. Many of these compounds can be viewed as fragments derived from the removal of the X-substituent from a 4,X-disubstituted-2-deoxystreptamine aminoglycoside, eg, neamine [34051-04-2/ C₁₂H₂ N₄ O₅ derived from paromomycin I or II (discussed below) by hydrolysis at the 5-position, tobramine [34051-04-2/ C₁₂H₂ N₄ O₅ (nebramine) derived from tobramycin (4) by hydrolysis at the 6-position, and gentamine C_{1a} [35025-95-7/ C₁₂H₂ N₄ O₅, derived from gentamicin C_{1a} (3, R = R' = H) by hydrolysis at the 6-position. Some of these compounds are found as fermentation products; alternatively, they can be obtained by chemical hydrolysis of the parent antibiotic. In general, however, the antibacterial activity is poor. An exception is apramycin (14), isolated from *Streptomyces tenebrarius*, which has respectable antibacterial activity and is resistant to the actions of some aminoglycoside-inactivating enzymes (129,130). For more details concerning this subclass of derivatives, see references 122 and 125.

Derivatives Containing a 5-Monosubstituted-2-deoxystreptamine Moiety. Few derivatives of this type are known. One is hygromycin B (15) isolated from *Streptomyces hygroscopicus* and *Streptomyces eurodicus* (131–133). The antibacterial activity is poor, but hygromycin B is reported to have anthelmintic activity (see ANTIPARASITIC AGENTS, ANTHELMINTICS).

Derivatives Containing a 4,5-Disubstituted-2-deoxystreptamine Moiety. The first of this subclass to be isolated were the neomycins (B (9) and C), followed by paromomycin I [7542-37-2/ C₂₃H₄₅N₅O₁₄, and paromomycin II [51795-47-2/ C₂₃H₄₅N₅O₁₄. The paromomycins are produced by a *Streptomyces rimosus* strain and have the same structures as neomycins B and C, respectively, except that the 6'-substituent is a hydroxy instead of an amino group (33,134–136). A closely related compound is lividomycin B [37636-51-4/ C₂₃H₄₅N₅O₁₃, which has the structure of neomycin B but the 3'-position is unsubstituted, instead of having a hydroxy group, and the 6'-substituent is a hydroxy (137–139). All these derivatives have significant antibacterial activity, but potency is lower than that of gentamicin and all are inactivated by AAC(3). The paromomycins are inactive against *P. aeruginosa* strains.

A related series of aminoglycosides have a structure similar to neomycin B, except that the sugar residue attached to the ribofuranosyl ring at 3'' is missing. The parent compound ribostamycin (16, R = H) was isolated from *Streptomyces ribosidificus* (140,141). A modified version of this molecule, butirosin B (16, R = (S)-COCHOHCH₂CH₂NH₂) was isolated from *Bacillus circulans*. Butirosin B was the first aminoglycoside isolated from a bacterium (142–145) and it was found that, by virtue of the (S)-4-amino-2-hydroxybutyryl substituent on the 1-amino group, an expanded antibacterial spectrum and resistance to the inactivating enzymes AAC(3) and APH(3') had been obtained. This observation indicated that a modification at the 1-position on the molecule could influence enzyme-catalyzed events occurring at the 3- and 3'-positions and ultimately led to the preparation of amikacin. The (S)-3-amino-2-hydroxypropionyl substituent was found to have a similar effect, resulting in isepamicin. This work showed that structure manipulation could affect the biological properties of an aminoglycoside in a significantly favorable way, and thus was an important impetus to further structural modifications within the 4,5-disubstituted-2-deoxystreptamine class (122,125).

Derivatives Containing a 4,6-Disubstituted-2-deoxystreptamine Moiety. Examples of this class are the kanamycin complex, consisting primarily of A (5, R = H), B (7, R = R' = OH), and C. Kanamycin C has the same structure as B except that hydroxy replaces the 6'-amino group (146). The members of the nebramycin complex are closely related structurally to the kanamycins (125). The most important are nebramycin factor 6, which is tobramycin (4), and nebramycin factor 5, which is kanamycin B (7, R = R' = OH). Kanamycin A was introduced into medical practice and still sees limited use, even though resistance to it is widespread and activity against *P. aeruginosa* strains is poor. Structural modifications of the kanamycins have been extensively investigated (120) and the most notable outcome of this work were the discoveries of amikacin (5, R = (S)-COCHOHCH₂CH₂NH₂) and dibekacin (7, R = R' = H). Many qualitative structure–activity correlations were found from these studies (120,122,123).

In general, acylation of any of the 3-, 2', 6'-, or 3''-amino groups greatly reduces antibacterial activity (147). However, acylation of the 1-amino group with one of a very limited number (148,149) of acyl groups, most notably, (S)-4-amino-2-hydroxybutyryl and (S)-3-amino-2-hydroxypropionyl, confers

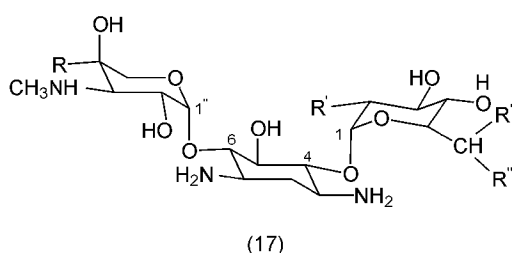
greatly improved resistance to bacterial inactivation reactions catalyzed by APH(3'), ANT(2''), and AAC(3), but not to others such as those of some isozymes of AAC(6') and ANT(4'). The 1-*N*-(2-aminoethanesulfonyl) derivatives have also been reported to have similar properties (150). Resistance to AAC(6') was improved somewhat in the formimidoyl and acetimidoyl derivatives of amikacin, but at a cost in potency (151). Interestingly, the 1-*N*-palmitoyl-3''-trifluoroacetyl derivatives of several aminoglycosides have been reported to have antiviral activity (152).

Monoalkylation using small alkyl groups of the 1-, 2'- and 3''-amines tends to reduce potency somewhat, whereas alkylation of the 3-amino group reduces activity considerably (147). 1-*N*-Alkylation, as in the case of 1-*N*-acylation, can lead to resistance to some bacterial resistance reactions, eg, 1-*N*-ethyl kanamycin A (153) has some resistance to APH(3'), ANT(2''), and AAC(3). Butakacin [59733-86-7] C₂₂H₄₅N₅O₁₂, the 1-*N*-(5)-2-hydroxy-4-aminobutyl derivative of kanamycin A (154), has antimicrobial properties similar to amikacin. A similar effect was seen with the 1-*N*-(1,3-dihydroxy-2-propyl) derivative of kanamycin B, propikacin [66887-96-5] C₂₁H₄₃N₅O₁₂ (155). Methylation of the 6'-amine reduces susceptibility to AAC(6') (156).

Removal of the hydroxyl groups from the 3'-, 4'-, 5-, or 6''-positions does not severely compromise antibacterial activity (157) and, in the case of 3' and 4', can protect from the action of APH(3') and ANT(4'). This type of modification is incorporated naturally in tobramycin (4) and semisynthetically in dibekacin (7, R = R' = H), resulting in significantly improved activity against *P. aeruginosa*. Perhaps surprisingly, 5,2',3',4',6''-hexadeoxykanamycin A is fully active, and even the 5,2',3',4',2'',4'',6''-heptadeoxy derivative retains some activity (158). The 2''-hydroxy appears to be the most important for activity (159,160). Removal of the 6'-hydroxy from kanamycin C, however, is detrimental (161) and the introduction of a 3'-fluoro in place of the 3'-hydroxy increases activity somewhat (162). Removal or epimerization of the 5-hydroxy of kanamycin B reduces antibacterial potency somewhat (163). When the 6''-hydroxy of kanamycin B has a carbamoyl group, the resulting derivative is the naturally occurring (*S. tenebrarius*) nebramycin factor 4 which has significant activity (164). In amikacin, replacement of the 6''-hydroxy with a fluorine decreases activity somewhat (165).

The 1-epi analogue of tobramycin (4) was slightly less active than the parent, but the 3-epi was almost inactive (166). Epimerization at the 1-position had a more detrimental effect with kanamycin A (166,167).

Four members of the gentamicin complex have been mentioned: B (8, R = H), C₁ (3, R = R' = CH₃), C_{1a} (3, R = R' = H), and C₂ (3, R = CH₃, R' = H). Gentamicin A [13291-74-2] C₁₈H₃N₄O₁₀ (17, R = R'' = H, R' = NH₂, R''' = OH), gentamicin X₂ [36889-17-5] (17, R = CH₃, R' = NH₂, R'' = H, R''' = OH), and gentamicin B₁ [36889-16-4] C₂₀H₄₀N₄O₁₀ (17, R = R'' = CH₃, R' = OH, R''' = NH₂) are representative of other members that have been isolated (168).



In addition to being antibacterial agents, although not as good as the C₁ + C_{1a} + C₂ combination, these compounds are reported to have antiprotozoal and anthelmintic activity. Many structure–activity correlations can be made within the gentamicin series (120,122,123).

1-*N*-Monoalkylation of members of the gentamicin–sisomicin group has been productive. This modification provides resistance to ANT(2'') and AAC(3) (123). Netilmicin (6, R = CH₂CH₃), which is 1-*N*-ethyl-sisomicin, is the most noteworthy example. Methylation of the 6'-amine confers resistance to some AAC(6') isozymes, eg, micronomicin [52093-21-7] C₂₀H₄₁N₅O₇ (sagamycin, gentamicin C_{2b}), the naturally occurring 6'-*N*-methyl derivative of gentamicin C_{1a}. The addition of a methyl group to the 6'-carbon, as in verdamicin, has a similar effect. Also, alkylation of the 2'-amino group can provide resistance to AAC(6') (123).

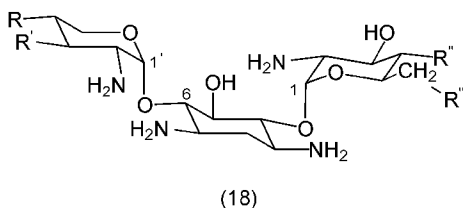
As in the kanamycin series, an α -hydroxy- ω -aminoacyl group on the 1-amino moiety of a number of gentamicin–sisomicin analogues confers activity against resistant bacterial strains (169). Isepamicin (8, R = (5)-COCHOHCH₂NH₂) is the primary example of this type of modification. In contrast to the kanamycins, 1-*N*-acetyl sisomicin was resistant to inactivation by AAC(3) and ANT(2'') (170). Other active 1-*N*-acylated derivatives have also been described (171,172). The naturally occurring 2'-*N*-formylsisomicin is considerably less active overall than sisomicin itself (173). Guanylation of the 1-, 3-, 2'-, or 6'-amines of gentamicin C components generally reduced potency (174); 2'-*N*-guanylgentamicin C₁ was less nephrotoxic in rats than gentamicin (175).

Considerable variation at the 2', 3', 4', 5' and 6' positions can be tolerated. For example, sisomicin (6, R = H) can be considered to be a 4',5'-dehydro derivative of gentamicin C_{1a}, and the related verdamicin [49863-48-1] C₂₀H₃₉N₅O₇, isolated from *Micromonospora grisea* (176), is the 4',5'-dehydro derivative of gentamicin C₂ (3, R = CH₃, R' = H). The 2'-position can be H, OH, or NH₂, as indicated by gentamicins C₂ and B₁ (169), the 3'-position can be H or OH, the 4'-position can be H or OH, and the 6'-position can carry an OH, NH₂, or NHCH₃, and may or may not have a C-methyl.

The 3''-methylamino in gentamicin C₂ can be changed to amino, ethylamino, *n*-propylamino, or *n*-butylamino with little change in antibacterial activity (177).

1-Deamino- and 1-deamino-1-hydroxy- analogues in the gentamicin series have been obtained by isolation and synthesis (178–180). These derivatives have weak antibacterial activity, although the 1-epi analogues of gentamicin C₁, netilmicin, and sisomicin are highly active (180).

The seldomycin complex, represented by seldomycin factor 1 [56276-04-1] C₁₇H₁₄N₄O₁₀ (18, R = R' = R'' = R''' = OH), seldomycin factor 3 [56276-05-2] C₁₇H₃₅N₅O₉ (18, R = R' = R'' = OH, R''' = NH₂), and seldomycin factor 5 [56276-26-7] C₁₈H₃₈N₅O₇ (18, R = OCH₃, R' = R'' = NH₂, R''' = H), were isolated from *Streptomyces hofmansi* (181,182). Of these, factor 5 has the best antibacterial activity, and is comparable in potency to kanamycin A (5, R = H). 3'-Deoxyseldomycin factor 5 (183) was found to be more active than the parent compound, while the 3'-epi analogue was less active (184).



Derivatives Containing a Modified 4,6-Disubstituted-2-deoxystreptamine Moiety. Mutasynthesis is the term used to refer to the process of employing mutated intermediate-requiring organisms to prepare derivatives that would be difficult to obtain by synthetic or semisynthetic means (117,185–188). Whereas this approach has been used to obtain aminoglycoside analogues, the primary contribution has been as a means to vary the 2-deoxystreptamine portion of the molecule. The most significant compound found by this approach is 5-episisomicin, which is produced by a

the treatment of gram-negative infections in the compromised patient. Semisynthetic modifications of naturally occurring compounds have yielded derivatives with greatly enhanced resistance to bacterial inactivation mechanisms without altering the basic antimicrobial spectrum. The principal factors limiting aminoglycoside usage are nephrotoxicity and ototoxicity. To date, structural modification has not been able to completely dissociate toxicity from antibacterial activity. Current research in the aminoglycoside field is focused on the reduction of toxicity through less frequent dosing, liposomal formulations, and coadministration of toxicity inhibitors.

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ANTIBIOTICS, ANTHRACYCLINES.

See CHEMOTHERAPEUTICS, ANTICANCER.

ANSAMACROLIDES

The ansamacrolides or ansamycins are a family of antibiotics characterized by an aliphatic ansa-bridge that connects two nonadjacent positions of an the aromatic nucleus (1,2). Ansamacrolides can be divided into two groups based on the nature of the aromatic nucleus. One group contains a naphthoquinoid nucleus and includes the streptovaricins, the rifamycins, tolypomycin, the halomycins, the naphthomycins, actamycin, the diastovaricins, kanglemycin, awamycin, and ansathiazin. The other group contains a benzoquinoid nucleus and includes geldanamycin, the maytansinoids, the herbimycins, the macbecins, the mycotrienins, the trienomycins, the ansatrienins, and the ansamitocins. Table 1 lists the naturally occurring ansamacrolides and some of their physical properties. Table 2 summarizes the biological activity of these antibiotics.

Table 1. Properties of the Ansamacrolides

Ansamacrolide	CAS Registry Number	Producing organism	Molecular formula	MP, °C	[α] _D ^a	Structu re no.	Referen ce
<i>Naphthoquinoid</i>							
streptovaricin A	[23344-16-3]	<i>Streptomyces spectabilis</i>	C ₄₂ H ₅₃ NO ₁	233–243	+610	(4)	3
streptovaricin B	[11031-82-6]	<i>Streptomyces spectabilis</i>	C ₄₂ H ₅₃ NO ₁₅	187–189	+576	(5)	3
streptovaricin C	[23344-17-4]	<i>Streptomyces spectabilis</i>	C ₄₀ H ₅₁ NO ₁₄	189–191	+602	(6)	3
streptovaricin D	[32164-26-4]	<i>Streptomyces spectabilis</i>	C ₄₀ H ₅₁ NO ₁₃	172–175	+590.3	(7)	3
streptovaricin E	[35413-63-9]	<i>Streptomyces spectabilis</i>	C ₄₀ H ₄₉ NO ₁₄	198–202	+412.3	(8)	3
streptovaricin F _G ^b	[35512-37-9]	<i>Streptomyces spectabilis</i>	C ₃₉ H ₄₇ NO ₁₄	222–224	+488 ^c	(12)	3
streptovaricin G	[11031-85-9]	<i>Streptomyces spectabilis</i>	C ₄₀ H ₅₁ NO ₁₅	190–192	473	(9)	3
streptovaricin J	[52275-61-3]	<i>Streptomyces spectabilis</i>	C ₄₂ H ₅₃ NO ₁₅	177–180	+436	(10)	3
streptovaricin K	[23344-16-3]	<i>Streptomyces spectabilis</i>	C ₄₂ H ₅₃ NO ₁	162–165		(11)	4
streptovaricin U	[74200-47-8]	<i>Streptomyces spectabilis</i>	C ₃ H ₄₉ NO ₁₀	115–140	110 ^c	(13)	5
rifamycin B	[13929-35-6]	<i>Nocardia mediterranei</i> n. sp. <i>Streptomyces tohyophorus</i>	C ₃₉ H ₄₉ NO ₁₄	160–164 ^d	11 ^c	(22)	6,7
rifamycin O	[14487-05-9]	<i>Streptomyces mediterranei</i> No. 4107 A ₂	C ₃₉ H ₄₇ NO ₁₄	160 ^d	+71.5 ^e	(23)	6,8
rifamycin S	[13553-79-2]	<i>Nocardia mediterranei</i> n. sp.	C ₃₇ H ₄₅ NO ₁₂	146–147	+462	(24)	6,9
rifamycin SV	[6998-60-3]	<i>Nocardia mediterranei</i> mutant ATCC 21271	C ₃₇ H ₄₇ NO ₁₂	140 ^d	4 ^c	(25)	6,10
rifamycin Y	[15271-73-5]	<i>Nocardia mediterranei</i>	C ₃₉ H ₄₇ NO ₁₅		+325	(29)	11
rifamycin L	[26117-02-2]	<i>Nocardia mediterranei</i>	C ₃₉ H ₄₉ NO ₁₄	152–153 ^d		(28)	12
rifamycin W	[53904-81-7]	<i>Nocardia mediterranei</i> mutant 126	C ₃₅ H ₄₅ NO ₁₁			(30)	13,14
rifamycin R	[59264-04-9]	<i>Nocardia mediterranei</i> mutant ATCC 31066	C ₃₇ H ₄₅ NO ₁₃			(27)	15
rifamycin P	[59232-87-0]	<i>Nocardia mediterranei</i> mutant ATCC 13685	C ₃₈ H ₄ N ₂ O ₁₁			(31)	16
rifamycin Q	[59232-88-1]	<i>Nocardia mediterranei</i> mutant ATCC 13685	S C ₃₉ H ₄₈ N ₂ O ₁₂			(32)	16
rifamycin verde	[72428-95-6]	<i>Nocardia mediterranei</i> mutant ATCC 13685	S C ₃₉ H ₄ N ₂ O ₁₂			(33)	16
rifamycin G	[59996-09-7]	<i>Nocardia mediterranei</i>	S C ₃ H ₄₇ NO ₁₂	250–252		(26)	17
tolypomycin Y	[23412-26-2]	<i>Streptomyces tohyophorus</i>	C ₄₃ H ₅₄ NO ₁₄	120	+326 ^f	(48)	7
halomycin A	[56411-51-9]	<i>Micromonospora halophytica</i>	C ₄₃ H ₅₈ N ₂ O ₁₃	192–194	+100.5	(54)	18
halomycin B	[54356-09-1]	<i>Micromonospora halophytica</i>	C ₄₃ H ₅₈ N ₂ O ₁₂	178–182	+73.1 ^c	(55)	19,20
halomycin C	[64419-06-3]	<i>Micromonospora halophytica</i>	C ₄₃ H ₅₈ N ₂ O ₁₃		+153	(56)	18
naphthomycin A	[55557-40-9]	<i>Streptomyces collinu</i> Lindenbein T _b 105	C ₄₀ H ₄ ClNO	ca 200	+432	(59)	21,22
naphthomycin B	[86828-40-9]	<i>Streptomyces galbus</i> T _b 353	⁹ C ₃₉ H ₄₄ ClNO	156–165	+412	(60)	23
naphthomycin C	[86825-87-8]	<i>Streptomyces diastatochromogenes</i> T _b 1892	⁹ C ₃₉ H ₄₅ NO ₉		+117.7	(61)	23
naphthomycin D	[105225-04-5]	<i>Streptomyces</i> T _b 2357	C ₄₀ H ₄₇ NO ₁₀		+323	(62)	22
naphthomycin E	[105225-03-4]	<i>Streptomyces</i> T _b 2357	C ₄₀ H ₄₇ NO ₉		+133.5	(63)	22
naphthomycin F	[105225-01-2]	<i>Streptomyces</i> T _b 2357	C ₄ H ₅ N ₂ O ₁₂		+333.4	(64)	22
naphthomycin G	[105225-02-3]	<i>Streptomyces</i> T _b 2357	C ₄₅ H ₅₄ N ₂ O ₁₂	188	+254 ^c	(65)	22
			S				

naphthomycin H ^g	[98525-20-3]	<i>Streptomyces</i> Y-83, 40369	C ₃₉ H ₄₄ ClNO	150	+21 ^b	(66)	24,25
naphthoquinomycin A	[101190-62-9]	<i>Streptomyces</i> S-1998	C ₄₀ H ₄₇ NO ₁₀	173–182	+212	(67)	25
naphthoquinomycin B	[101190-61-8]	<i>Streptomyces</i> S-1998	C ₄₀ H ₄₇ NO ₉ S	171–180	+541	(68)	25
actamycin	[76045-67-5]	<i>Streptomyces</i> E/784	C ₃₉ H ₄₅ NO ₁₀	190–192		(69)	26
diastovaricin I	[102281-52-7]	<i>Streptomyces diastochromogenes (variabilicolor)</i>	C ₃₉ H ₄₅ NO ₁₀	237–238	+351 ^c	(70)	27
diastovaricin II	[102228-99-9]	<i>Streptomyces diastochromogenes (variabilicolor)</i>	C ₄₄ H ₅₂ N ₂ O ₁₂	160–164	+281 ^c	(71)	27
kanglemycin A	[114153-91-2]	<i>Nocardia mediterranei</i> var. <i>kanglensis</i> 1747-64	C ₅₀ H ₃ NO ₁₉	156 ^d	+31 ^{b,4} _c	(74)	28
awamycin	[87913-35-7]	<i>Streptomyces albolongus</i> C 46466	C ₃₈ H ₄₉ NO ₁₂	162–165	+949	(75)	29
ansathiazin	[105645-37-2]	<i>Streptomyces albolongus</i> C-46366	C ₃₇ H ₄₇ NO ₁₃	170–175	32	(76)	29
Benzoquinoid geldanamycin	[30562-34-6]	<i>Streptomyces hygroscopicus</i> var. <i>geldanus</i> var. <i>nova</i> (UC-5208)	C ₂₉ H ₄₀ N ₂ O ₉	252–255	+55	(77)	30
herbimycin A	[70563-58-5]	<i>Streptomyces hygroscopicus</i> AM-3672	C ₃₀ H ₄₂ N ₂ O ₉	230	+137	(82)	31,32
herbimycin B	[76207-83-5]	<i>Streptomyces hygroscopicus</i> AM-3672	C ₂₈ H ₃₈ N ₂ O ₈	229 ^d	+109	(83)	33
herbimycin C	[91700-92-7]	<i>Streptomyces hygroscopicus</i> AM-3672	C ₂₉ H ₄₀ N ₂ O ₉	203 ^d	+210	(84)	34
macbecin I	[73341-72-7]	<i>Nocardia</i> sp. C-14919 (N-2001)	C ₃₀ H ₄₂ N ₂ O ₈	187–188	+351	(90)	35,36
macbecin II	[73341-73-78]	<i>Nocardia</i> sp. C-14919 (N-2001)	C ₃₀ H ₄₄ N ₂ O ₈	148 ^d	+62	(91)	35,36
mycotrienin I	[82189-03-5]	<i>Streptomyces rishirensis</i> T-23	C ₃ H ₄₈ N ₂ O ₈	117	+92 ^c	(92)	37,38
mycotrienin II	[82189-04-6]	<i>Streptomyces rishirensis</i> T-23	C ₃ H ₅₀ N ₂ O ₈	151	+288 ^c	(93)	37–39
mycotrienol I	[81904-15-6]	<i>Streptomyces rishirensis</i> T-23	C ₂ H ₃₃ NO	94–95	+4.3 ^c	(95)	40
mycotrienol II	[87906-73-0]	<i>Streptomyces rishirensis</i> T-23C	C ₂ H ₃₅ NO	130–132	+273 ^c	(96)	40
20-O-methylmycotrienin II	[98873-82-6]	<i>Streptomyces rishirensis</i> T-23	C ₃₇ H ₅₂ N ₂ O ₈	128	+373 ^c	(94)	41
trienomycin A ^h	[97955-33-4]	<i>Streptomyces rishirensis</i> T-23 <i>Streptomyces</i> sp. No. 83-16	C ₃ H ₅₀ N ₂ O ₇	135	+174 ^c	(97)	41–43
trienomycin B	[100662-01-09]	<i>Streptomyces</i> sp. No. 83-16	C ₃₄ H ₄₈ N ₂ O ₇	124–126	+170 ^c	(98)	44
trienomycin C	[100662-01-9]	<i>Streptomyces</i> sp. No. 83-16	C ₃₄ H ₄₈ N ₂ O ₇	119.5–121.5	+186 ^c	(99)	44
ansatrienin A	[80111-47-3]	<i>Streptomyces collinus</i> strain T _b 1982	C ₃ H ₄₈ N ₂ O ₈			(100)	45
ansatrienin A ₂	[85819-32-4]	<i>Streptomyces collinus</i> strain T _b 1982	C ₃₄ H ₄ N ₂ O ₈	115 ^d	+11 ^{b,7} _d	(101)	46
ansatrienin A ₃	[85819-31-4]	<i>Streptomyces collinus</i> strain T _b 1982	C ₃₄ H ₄ N ₂ O ₈	117 ^d	+119.4	(102)	46
ansatrienin B	[80111-48-4]	<i>Streptomyces collinus</i> strain T _b 1982	C ₃₄ H ₄ N ₂ O ₈			(103)	45
maytansine	[35486-53-8]	<i>Maytenus ovatus</i> Loes. <i>Maytenus serrata</i> (Celastraceae)	C ₃₄ H ₄ ClN ₃	171–172	145	(104)	47,48
maytanprine	[38997-09-0]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek <i>Maytenus serrata</i> (Celastraceae)	C ₃₅ H ₄₈ ClN ₃	169–170	125	(106)	48,49
maytanbutine	[38997-10-3]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek <i>Maytenus serrata</i> (Celastraceae)	C ₃ H ₅₀ ClN ₃	170–171	122	(107)	48,49
maytanvaline	[52978-27-5]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek	C ₃₇ H ₅₂ ClN ₃	175–176.5	135	(105)	48,50
maysine	[52978-28-6]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek	C ₂₈ H ₃₅ ClN ₂	137–141	173 ^f	(110)	48,50
normaysine	[52978-29-7]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek	C ₂₇ H ₃₃ ClN ₂	187–188	217 ^f	(111)	48,50
maysenine	[52978-30-0]	<i>Maytenus buchananii</i> (Loes.) R. Wilczek	C ₂₇ H ₃₃ ClN ₂	184–185	57 ^f	(112)	48,50
colubrinol	[50657-35-5]	<i>Colubrina texensis</i> Gray (Rhamnaceae) <i>Trewia nudiflora</i> L. (Euphorbiaceae)	C ₃ H ₅₀ ClN ₂	194–196	94	(114)	51,52
colubrinol acetate	[50499-79-1]	<i>Colubrina texensis</i> Gray (Rhamnaceae)	C ₃ H ₅₀ ClN ₂	179–182	127	(115)	51
maytanacine	[57103-69-2]	<i>Putterlickia verrucosa</i> Szysyl. (Celastraceae)	C ₃₀ H ₃₉ ClN ₂	234–237	119	(109)	48,53
maytansinol	[57103-68-1]	<i>Putterlickia verrucosa</i> Szysyl. (Celastraceae)	C ₂₈ H ₃₇ ClN ₂	173–174.5	309	(113)	48,53
maytanbutacine	[62414-95-3]	<i>Maytenus serrata</i> (Celastraceae)	C ₃₄ H ₄₅ ClN ₂	253–255	90 ^f	(108)	48
normaytansine	[75983-74-3]	<i>Maytenus buchananii</i>	C ₃₂ H ₄₁ ClN ₂	166–167		(116)	54
trewiasine	[78987-26-5]	<i>Trewia nudiflora</i> L. (Euphorbiaceae)	C ₃₇ H ₅₂ ClN ₃	182–185	94	(117)	55
dehydrotrewiasine	[78987-27-6]	<i>Trewia nudiflora</i> L. (Euphorbiaceae)	C ₃₇ H ₅₀ ClN ₃	165–170	90	(118)	55

demethyltrewiasine	[78987-28-7]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{11} $\text{C}_3\text{H}_{50}\text{ClN}_3$	129–142	126	(119)	55
trenudine	[82390-94-1]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{11} $\text{C}_3\text{H}_{48}\text{ClN}_3$	200–205 ^d	114	(121)	55,56
trefflorine	[82390-93-0]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{13} $\text{C}_3\text{H}_{48}\text{ClN}_3$	205–208 ^d	138	(120)	55,56
normaytancyprine	[84123-43-3]	<i>Putterlickia verrucosa</i> Szyszl. (<i>Celastraceae</i>)	O_{12} $\text{C}_{37}\text{H}_{50}\text{ClN}_3$	143–145		(125)	57
N-methyltrenudone	[82400-19-9]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{10} $\text{C}_{37}\text{H}_{48}\text{ClN}_3$	192–197 ^d	110	(122)	56
10-epitrewiasine	[88198-82-7]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{10} $\text{C}_{37}\text{H}_{53}\text{ClN}_3$	159–162	48	(123)	52
nortrewiasine	[88147-94-8]	<i>Trewia nudiflora</i> L. (<i>Euphorbiaceae</i>)	O_{11} $\text{C}_3\text{H}_{50}\text{ClN}_3$	155–158	58	(124)	52
ansamitocin P-3	[66584-72-3]	<i>Nocardia</i> sp. C-15003	O_{11} $\text{C}_{32}\text{H}_{43}\text{ClN}_2$	190–191	136	(127)	58
ansamitocin P-3'	[66547-09-9]	<i>Nocardia</i> sp. C-15003	O_9 $\text{C}_{32}\text{H}_{43}\text{ClN}_2$	182–185	134	(128)	58
ansamitocin P-4	[66547-10-2]	<i>Nocardia</i> sp. C-15003	O_9 $\text{C}_{33}\text{H}_{45}\text{ClN}_2$	177–180	142	(129)	58
ansamitocin PND-0	[77353-66-3]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_9 $\text{C}_{27}\text{H}_{35}\text{ClN}_2$	189–191 ^d		(131)	59
ansamitocin PND-1	[77353-67-4]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_8 $\text{C}_{29}\text{H}_{37}\text{ClN}_2$		55.8 ^f	(132)	59
ansamitocin PND-2	[77353-68-5]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_9 $\text{C}_{30}\text{H}_{39}\text{ClN}_2$		56.3 ^f	(133)	59
ansamitocin PND-3	[77353-69-6]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_9 $\text{C}_{31}\text{H}_{41}\text{ClN}_2\text{O}_9$	226–228 ^d	57.1 ^f	(134)	59
ansamitocin PND-4	[77353-70-9]	<i>Nocardia</i> sp. C-14482 mutant N-1231	$\text{C}_{32}\text{H}_{43}\text{ClN}_2$		56.6 ^f	(135)	59
ansamitocin PHM-1	[78619-40-6]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_9 $\text{C}_{30}\text{H}_{39}\text{ClN}_2$			(136)	59
ansamitocin PHM-2	[78619-39-3]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{31}\text{H}_{41}\text{ClN}_2$			(137)	59
ansamitocin PHM-3	[78619-38-2]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{32}\text{H}_{43}\text{ClN}_2$	192–194 ^d	148 ^f	(138)	59
ansamitocin PHM-4	[78630-36-1]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{33}\text{H}_{45}\text{ClN}_2$		148 ^f	(139)	59
ansamitocin P-4-βHY	[78619-41-7]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{33}\text{H}_{45}\text{ClN}_2$	201–203 ^d		(140)	59
ansamitocin P-4-γHY	[78709-93-0]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{33}\text{H}_{45}\text{ClN}_2$	205–207 ^d		(141)	59
ansamitocin PND-4-βHY	[78619-43-9]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{32}\text{H}_{43}\text{ClN}_2$			(142)	59
ansamitocin deClQ-O	[78630-38-3]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_{10} $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_7$			(145)	59
ansamitocin QND-O	[78619-44-0]	<i>Nocardia</i> sp. C-14482 mutant N-1231	$\text{C}_{27}\text{H}_{35}\text{ClN}_2$			(144)	59
ansamitocin deClQND-0	[78630-37-2]	<i>Nocardia</i> sp. C-14482 mutant N-1231	O_7 $\text{C}_{27}\text{H}_3\text{N}_2\text{O}_7$			(143)	59
ansamitocin PHO-3	[62414-96-4]	<i>Nocardia</i> sp. C-14482 mutant N-1231	$\text{C}_{32}\text{H}_{43}\text{ClN}_2$	227–229 ^d	95.9 ^f	(130)	59
ansamitocin P-2	[57103-70-5]	<i>Nordardia</i> sp. C-15003	O_{10} $\text{C}_{31}\text{H}_{41}\text{ClN}_2$ O_9	188–190 ^d	127	(126)	58

^a Determined in CHCl₃ unless otherwise noted.
^b Originally called streptovaricin F.
^c Determined in methanol.
^d Decomposes at this temperature.
^e Determined in dioxane.
^f Determined in ethanol.
^g Same as naphthoquinomycin C.
^h Same as 23-deoxymycotrienin II.

Table 2. Biological Activity of the Ansamacrolides

Ansamacrolide	Biological activity
streptovaricins	antibacterial (gram-positive and mycobacteria), antiviral, inhibitors of reverse transcriptase
rifamycins	antibacterial (gram-positive, gram-negative, and mycobacteria), antiviral, inhibitors of reverse transcriptase
tolypomycins	antibacterial (gram-positive)
halomycins	antibacterial (gram-positive)
naphthomycins	antibacterial (gram-positive), vitamin K antagonist
actamycins	inhibitors of fatty acid synthesis
diastovaricins	antileukemic
kanglemycins	antibacterial (gram-positive)
awamycins	antibacterial (gram-positive), antitumor
ansathiazins	antibacterial (gram-positive)
geldanamycins	antiprotozoal, herbicidal, inhibitors of reverse transcriptase
herbimycins	herbicidal, antitumor, antiviral, inhibitors of tyrosine kinase
macbecins	antibacterial (gram-positive), antiprotozoal, antifungal, antitumor
mycotrienins	antifungal
trienomycins	antitumor
ansatrienins	antifungal
maytansinoids	antileukemic, antitumor
ansamitocins	antiprotozoal, antifungal, antitumor

Naphthoquinoids

Streptovaricins. The streptovaricins are produced by *Streptomyces spectabilis* n. sp. (60,61) and are isolated as a crude complex (62,63). Substance B 44 P, isolated from *Streptomyces* B 44-P1, was shown to be identical with the streptovaricins (64). Chemical degradation studies carried out on streptovaricins A and C, which are the primary components of the crude complex, yielded substances shown in Figure 1. Streptovaricin A (4), consumes two moles of sodium periodate to yield varicinal A [21913-68-8] (1), C₁₃H₂₀O₇, which accounts for the aliphatic portion of the molecule, and prestreptovarone [58074-37-6] (2), C₂₀H₂₉NO₉, which accounts for the aromatic chromophore of the streptovaricins (Fig. 2). Streptovaricin G (9) is the only other streptovaricin that yields prestreptovarone upon treatment with sodium periodate. Treatment of streptovaricins A (4), B (5), C (6), E (8), and G (9) with sodium periodate and osmium tetroxide yields streptovarone [36108-44-8] (3), C₂₄H₂₃NO₉, which is also produced by the reaction of prestreptovarone with sodium periodate and osmium tetroxide (4,65). A number of aliphatic products were isolated from the oxidation of streptovaricin C and its derivatives (66).

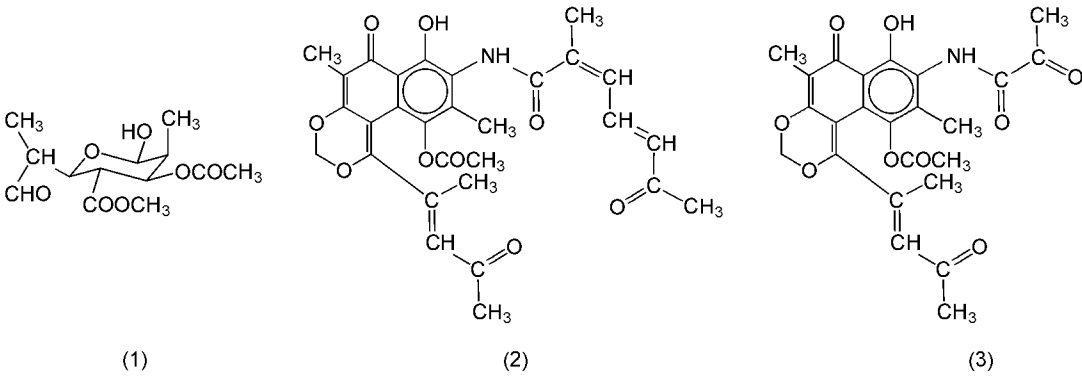


Fig. 1. Products from the chemical degradation of streptovaricins A and C.

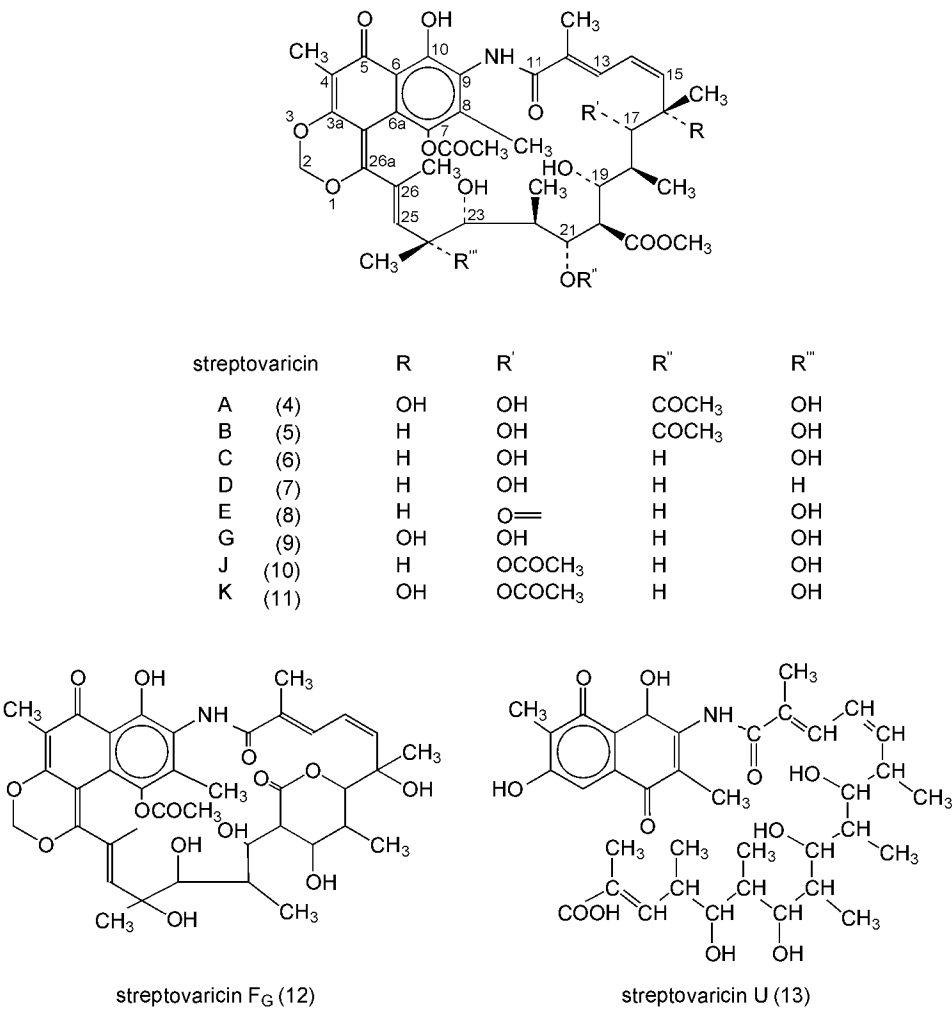


Fig. 2. Structures of the streptovaricins.

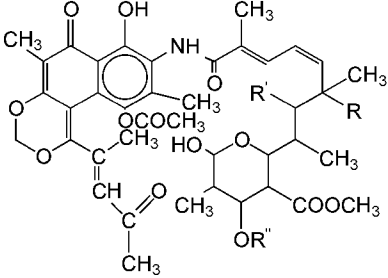
The relationships among the various streptovaricins were shown by the following reactions: streptovaricin E (8) converts to streptovaricin C (6) upon treatment with sodium borohydride; streptovaricins A (4), G (9), and K (11) yield the same triacetate derivative upon acetylation; streptovaricins B (5), C (6), and J (10) yield the same tri- and tetraacetate derivatives upon acetylation; streptovaricin G (9) converts to streptovaricin F_G (12) upon treatment with base (4). The open-chain streptovaricin U (13) has also been isolated from the streptovaricin complex (5).

The structures of the streptovaricins were confirmed by x-ray crystallographic studies (67,68). The absolute configuration of the ansa-bridge is 6(R), 7(R), 8(R), 9(R), 10(S), 12(R), 13(S), and 14(R) with a helicity of *P* (69). Complete mass spectral (4,70,71) and ¹³C nmr studies have been reported (72).

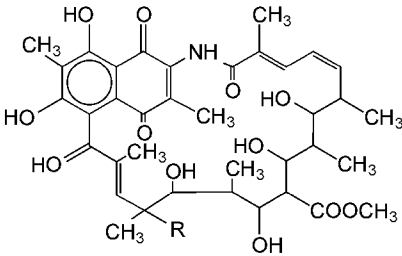
Chemical Properties and Derivatives. All of the streptovaricins except streptovaricin D (7) react with one mole of sodium periodate to yield the corresponding streptovals (4), shown in Table 3. The streptovaricins undergo thermal isomerization to the corresponding atropisostreptovaricins (73). In the natural streptovaricins the ansa-bridge lies above the aromatic nucleus but in the atropisostreptovaricins this bridge lies below the aromatic nucleus. Most spectral properties of the isomers are nearly identical, but the optical rotations, although of approximately equal magnitude, are of opposite sign. If pyridine is used as the solvent, lactonized streptovaricins are obtained similar to streptovaricin F_G (12) as well as the atropisostreptovaricins.

Treatment of streptovaricin C or D with oxygenated concentrated ammonia–methanol solution yields damavaricin C (20) or D (21) through loss of the enol acetate and methylenedioxy groups (74) (Table 3). The damavaricins are related to the naturally occurring rifamycin W, and damavaricin D has been isolated from the streptovaricin complex. Besides damavaricins C and D, the basic methanolysis yields the corresponding atropisodamavaricins and lactonized damavaricins. The streptovaricins form acetonides and are hydrogenated to mixtures of di- and tetrahydro derivatives (4). Although few derivatives of the streptovaricins have been prepared, a large number of 19-*O*-substituted damavaricins (75) and lactonized damavaricins (76–78) have been reported. The synthesis of the naphthalene core of streptovaricin D has been accomplished (79) whereas several routes to the ansachain of the streptovaricins have been reported (80–83).

Table 3. Derivatives of the Streptovaricins

Compound	CAS Registry Number	Molecular formula	Structure number	R	R'	R''
<i>Streptovals</i>						
						
streptoval A	[60760-75-0]	C ₄₂ H ₅₁ NO ₁	(14)	OH	OH	COCH ₃
streptoval B	[60735-99-1]	C ₄₂ H ₅₁ NO ₁₅	(15)	H	OH	COCH ₃
streptoval C	[54955-14-5]	C ₄₀ H ₄₉ NO ₁₄	(16)	H	OH	H

streptoval E	[60736-00-7]	C ₄₀ H ₄₇ NO ₁₄	(17)	H	O	H
streptoval G	[60736-02-9]	C ₄₀ H ₄₉ NO ₁₅	(18)	OH	OH	H
streptoval J	[60736-03-0]	C ₄₂ H ₅₁ NO ₁₅	(19)	H	COCH ₃	H



Damavaricins						
damavaricin C	[58849-86-8]	C ₃₇ H ₄₇ NO ₁₃	(20)	OH		
damavaricin D	[59556-95-5]	C ₃₇ H ₄₇ NO ₁₂	(21)	H		

Biological Activity. The streptovaricins are mainly active against gram-positive organisms, and have very good activity against *Mycobacterium tuberculosis*, *M. leprae*, and *Staphylococcus aureus* infections in animals (60,84). The totally acetylated streptovaricins lose their antibacterial activity. Streptovaricin U has no antibacterial activity. Lactonization greatly reduces any biological activity a streptovaricin possesses. The antibacterial activities of the atropisostreptovaricins are about the same as the natural isomers. Although the damavaricins retain biological activity, they are not as active as the corresponding streptovaricins. However, many of the 19-*O*-substituted damavaricins exhibit greater antibacterial activity than the parent streptovaricins (76). The streptovals are also inactive as antibacterial agents (4).

The streptovaricins inhibit the reverse transcriptase of some RNA oncogenic viruses that may be involved in the process of viral transformation (see ANTIVIRAL AGENTS). The atropisostreptovaricins again have similar activities to the corresponding natural isomers. The streptovals and streptovarone exhibit greatly improved activity against reverse transcriptase relative to the streptovaricins (85), but their *in vitro* activities were low (86). The damavaricins also inhibit reverse transcriptase (4) as well as tumor cell growth (87).

Clinical studies with streptovaricins have been limited. The most significant toxicity reported in the clinical studies has been gastrointestinal disturbances. However, indications are that the toxicity does not result from the individual streptovaricins but from some impurity in some fermentation lots (85).

Assay Methods. The primary assay for the streptovaricins is the microbiological assay using the agar diffusion method or a turbidimetric procedure (60). The streptovaricins can also be identified by paper (60,88) or thin-layer chromatography (3).

Rifamycins. The rifamycins were first isolated from a broth of *Nocardia mediterranei* (the producing organism was originally identified as *Streptomyces mediterranei*). The rifamycins, the structures of which are shown in Figure 3, were originally designated as rifomycins. Only rifamycin B (22), which accounts for 10–15% of the crude complex, can be isolated easily as a stable, crystalline compound (6,89,90).

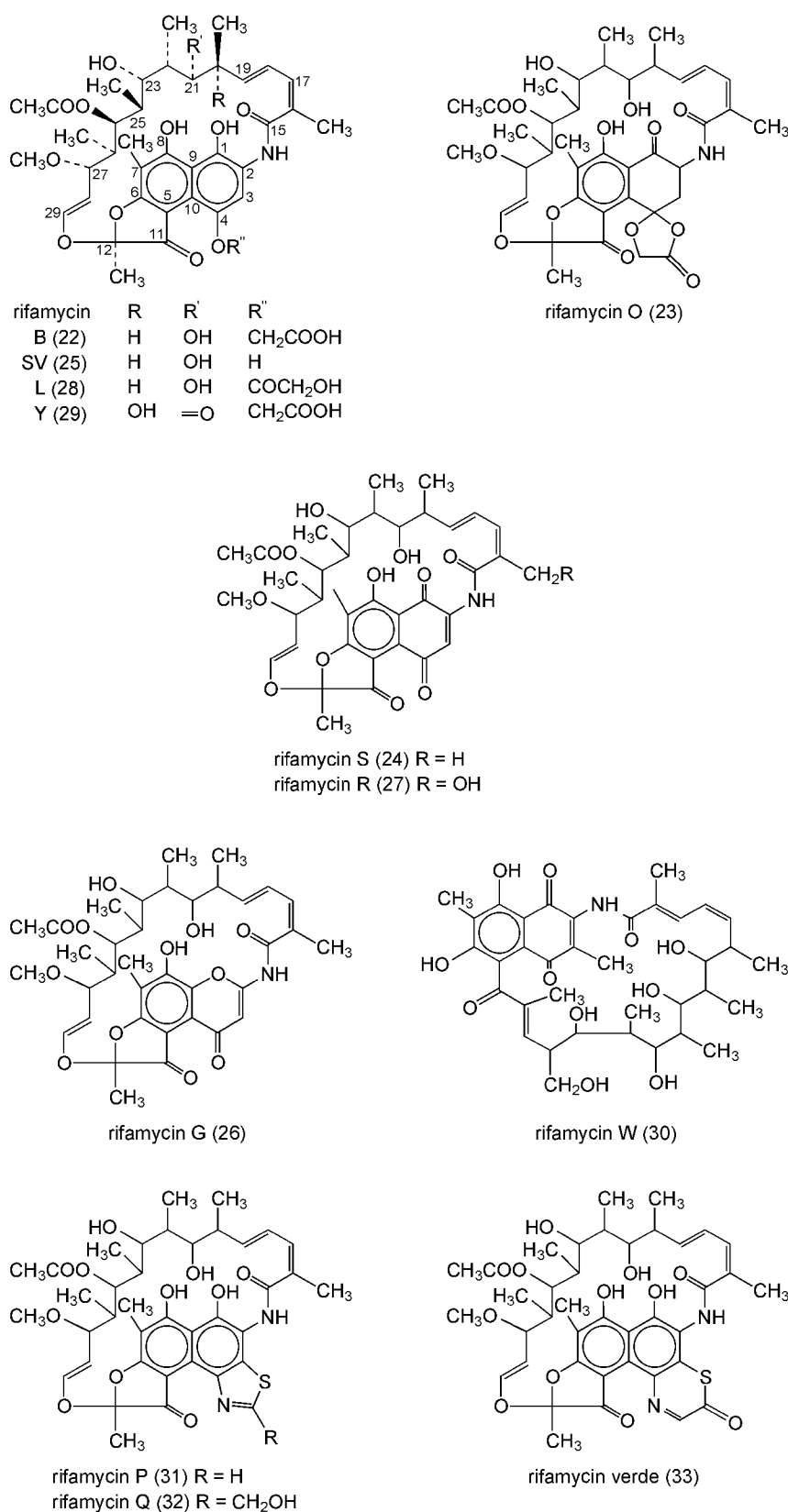


Fig. 3. Structures of the rifamycins.

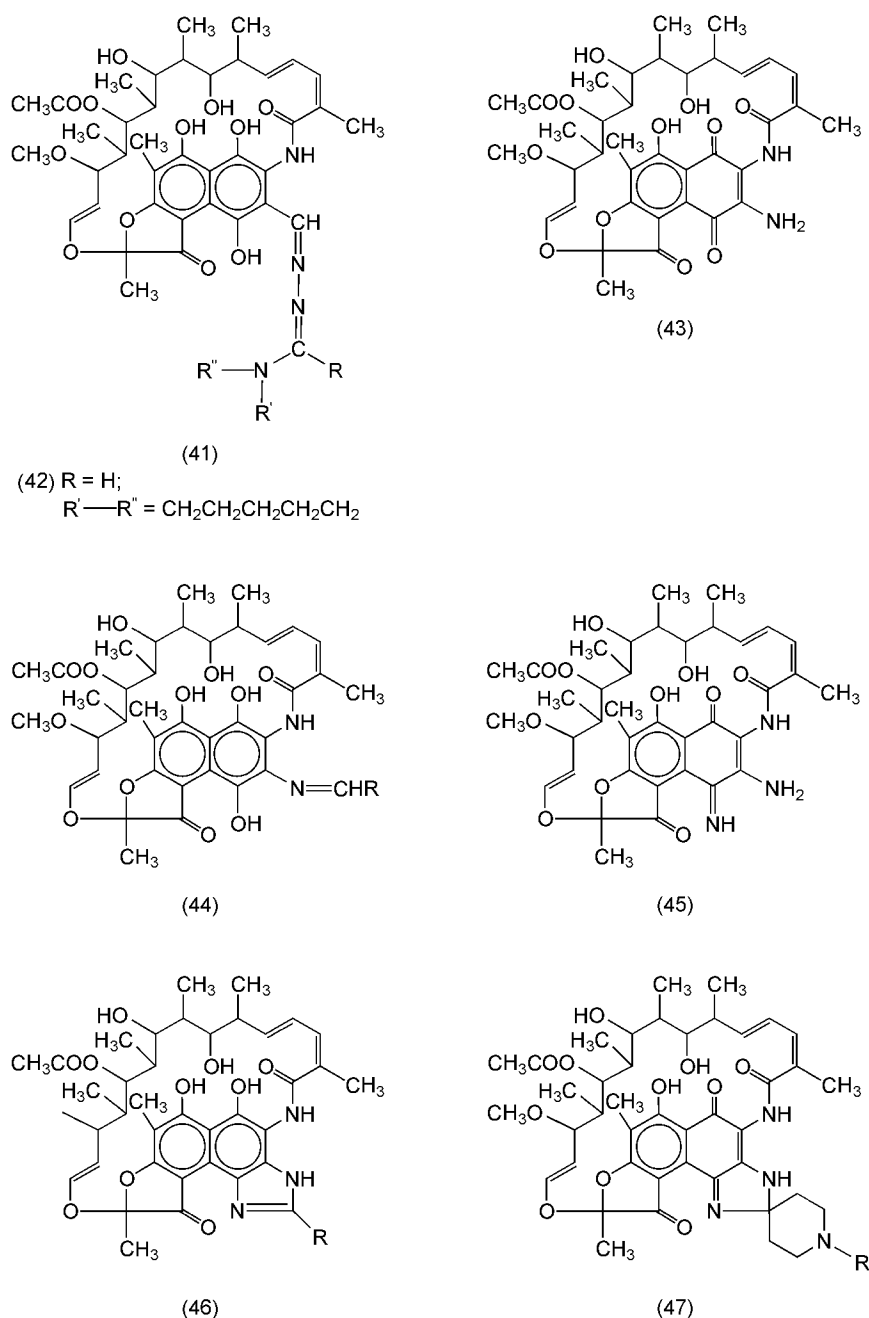
Difficulties encountered in the separation and stability of the individual rifamycins led to studies to increase the yield of individual components of the complex. The addition of sodium diethylbarbiturate to the fermentation medium of *N. mediterranei* resulted in the formation of rifamycin B as practically the only substance formed (91,92).

Rifamycin B (22) is oxidized by air to the more active rifamycin O (23) upon standing in solution. This reaction also occurs when rifamycin B is treated with a variety of oxidizing agents such as hydrogen peroxide. Rifamycin O can be reconverted to rifamycin B by treatment with ascorbic acid. Rifamycin O in turn can be hydrolyzed to the even more active rifamycin S (24) by the expulsion of glycolic acid. Rifamycin S can be reduced, using ascorbic acid, to rifamycin SV (25) and rifamycin SV can be oxidized to rifamycin S (5,93,94). Although rifamycins O and S were originally chemical derivatives of rifamycin B, microorganisms have been found that produce these rifamycins naturally.

Rifamycin G (26) is also isolated from the *Nocardia mediterranei* fermentation and appears to be a metabolic product of rifamycin S (17). Rifamycin R (27) is produced by a mutant of *N. mediterranei* (ATCC 31066) and appears to be biosynthesized from rifamycin S by the oxidation of the C-2 methyl group (15). Rifamycin L (28) is an oxidation product formed by incubating rifamycin S with washed mycelia of *N. mediterranei* (12). Rifamycin Y (29) is produced along with rifamycin B when this organism is cultured in the presence of diethylbarbituric acid (11). The amount of rifamycin Y produced was originally high, but through strain improvements, it is now produced in only small amounts (95). Rifamycin W (30) is produced by mutant 126 of *N. mediterranei* (13,14). The sulfur containing rifamycins P (31), Q (32), and verde (33) are produced by the mutant *Nocardia mediterranei* ATCC 31685 (16).

The structures of the rifamycins were arrived at by chemical degradation studies (1,4,96,97) and confirmed by x-ray crystallography (98–100). The absolute configuration of the ansa-bridge is 6(*S*), 7(*S*), 8(*R*), 9(*R*), 10(*R*), 11(*S*), 12(*R*), and 13(*S*) (101). Studies of ¹³C nmr (4,13,14,102–104) and ir (104) have been reported and mass spectra of the rifamycins have been obtained (105–107).

Chemical Properties and Derivatives. There have been thousands of rifamycin derivatives prepared in an attempt to obtain a broader

Fig. 4b. *Continued*

Treatment of rifamycin B (**22**) with amines, hydrazines, and alcohols yields the corresponding amides, hydrazides, and esters (**34**), respectively (4,6,108–110). The most active of this class is the *N,N*-diethyl derivative known as rifamide [2750-76-7], $C_{43}H_{58}N_2O_{13}$ (111). Rifamide is active against gram-positive bacteria and has very low toxicity (112–114). Good activity is exhibited against *M. tuberculosis*.

Rifamycin O (**23**) reacts with a variety of aromatic amines, hydrazines, amidrazones, and aminoguanidines to yield quinonimine derivatives (**35**). All of the derivatives show good activity against gram-positive bacteria. The condensation product with aminoguanidine, known as rifamycin AG, is a broad-spectrum antibiotic possessing good activity against gram-positive and gram-negative bacteria and *M. tuberculosis* (6,109,115).

Reaction of rifamycin S (**24**) with a variety of *o*-phenylenediamines and *o*-aminophenols produces a series of phenazines (**36**) and phenoxazines (**37**), respectively. Rifazine [10238-70-7] (**37**, $R = H$), $C_{43}H_{49}N_3O_{11}$, is the simplest of the phenazines (116–119).

Rifamycin S also undergoes conjugate addition reactions to the quinone ring by a variety of nucleophiles including ammonia, primary and secondary amines, mercaptans, carbanions, and enamines giving the C-3 substituted derivatives (**38**) of rifamycin SV (117,120,121). Many of the derivatives show excellent antibacterial properties (109,118,122,123). The 3-cyclic amino derivatives of rifamycin SV also inhibit the polymerase of RNA tumor viruses (123,124).

Treatment of rifamycin S with formaldehyde and secondary amines yields the 3-aminomethyl derivatives (**38**, $X = CH_2NR_2$) which are not of therapeutic interest (125). However, upon oxidation in acidic medium, the aminomethyl derivatives yield 3-formylrifamycin SV, also known as rifaldehyde [13292-22-3] (**38**, $X = CHO$), $C_{38}H_{47}NO_{13}$. Treatment of rifaldehyde with amines, hydrazines, hydroxylamines, and hydrazides yields a number of derivatives of the 3-formyl group having excellent biological activity (109,126–128). The most therapeutically useful derivative is the *N*-amino-*N'*-methylpiperazine hydrazone of rifaldehyde known as rifampin in the United States and rifampicin elsewhere.

Rifampicin [13292-46-1] (**39**), $C_{43}H_{58}N_4O_{12}$, is active against a variety of gram-positive and gram-negative bacteria; however, resistance develops rapidly if it is used alone (129–131). Rifampicin finds its greatest use in the treatment of tuberculosis (130,132–134). Because resistance develops rapidly, rifampicin is normally given in combination with other antituberculosis drugs, eg, isoniazid [54-85-3], $C_7H_7N_3O$ (130,132,135). Rifampicin has been used to treat nontuberculosis infections (136–138), with especially good activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* (139).

Rifampicin has also shown antiviral activity but at levels 500–1000 times greater than required for antibacterial activity (130,140–142). Rifampicin shows promise in the treatment of leprosy (130,143). A large number of rifampicinlike derivatives are potent inhibitors of reverse transcriptase (123,144–148).

Rifapentine (DL473) [61379-65-5] (**40**), $C_{47}H_{54}N_4O_{12}$, a piperazinyl hydrazone of 3-formyl rifamycin SV, is similar to rifampicin. Rifapentine has activity similar to rifampicin, but its half-life is much longer (149,150).

A number of oxime derivatives of rifaldehyde have been prepared. Many of these derivatives exhibit good activity against rifampicin-resistant organisms (151,152).

Another class of active derivatives prepared from rifaldehyde, are the 3-aminomethylazinomethyl rifamycins (**41**). This class of compounds is prepared by treating rifaldehyde with hydrazine to yield hydrazones of the 3-aldehyde of rifamycin SV (**38**, $X = CH = NNH_2$), which is further treated with a suitable chloroformiminium chloride or the dimethyl acetals of tertiary amides to yield (**41**) (153–155). The piperidine analogue known as FCE 22250 (**42**) was chosen for further studies because of low toxicity coupled with high activity and a long half-life.

Three new classes of rifamycin derivatives were prepared from the common intermediate 3-amino-rifamycin S [51756-80-0] (**43**), $C_{37}H_4N_2O_{12}$. Reduction of (**43**) in the presence of an aldehyde yields derivatives of the general formula (**44**). Reaction of (**43**) and ammonia in THF solution yields (**45**) [62041-01-4] which in turn can be converted to imidazo-rifamycins (**46**) or to spiro-piperidyl-rifamycins (**47**) by treatment with aldehydes under reducing conditions or with ketones, respectively. All three classes of derivatives have *in vitro* antibacterial activities comparable to those of rifampicin (156). The spiro-piperidyl-rifamycin rifabutin (LM 427) [72559-06-9] (**47**, $R = CH_2CH(CH_3)CH_3$), $C_{44}H_{52}N_4O_{11}$, showed good *in vitro* and *in vivo* activity against *Mycobacterium tuberculosis* (157) as well as displaying a broad spectrum of biological activity (158). It was also shown to be active against *M. aviumintracellulare* (159), which is frequently encountered in patients having acquired immune deficiency syndrome (AIDS). Rifabutin, used to treat AIDS patients having *Mycobacterium* infections, was shown to inhibit replication of human immunodeficiency virus type 1 (HIV-1) (160).

Modifications to the ansa-bridge of the rifamycins decreases the activity against gram-positive bacteria. Hydrogenation of the ansa-bridge double bonds increases the activity towards gram-negative bacteria as does removal of the C-11 acetate group (109).

Synthesis of the aromatic portion of rifamycin S has been accomplished (161) as has the ansa-bridge portion (162–164). Joining of these fragments resulted in rifamycin S total synthesis (165,166).

Biological Activity. The rifamycins are biologically active against gram-positive microorganisms and mycobacteria, particularly *M. tuberculosis* (6,167–170). At higher concentrations, the rifamycins are also active against gram-negative bacteria. The rifamycins show antiviral activity (140,141) and inhibit reverse transcriptase (171–173).

Rifamycin B is not biologically active but is spontaneously converted in aqueous solution to the active rifamycins O, S, and SV. Rifamycin SV was chosen for further studies because of its good *in vivo* activity, low toxicity, and solubility properties. Rifamycin SV is effective against a variety of infections as well as being active against tuberculosis and leprosy (168). Rifamycin P is the most active of the naturally occurring rifamycins (174).

Manufacture and Processing. Although fermentation procedures have not been reported, assumptions concerning fermentation media and optimal conditions have been made (95,174). The transformation of the biologically inactive rifamycin B to the biologically active rifamycin S is usually accomplished chemically. Several rifamycin B oxidases have been isolated that can enzymatically transform rifamycin B to rifamycin O, which is hydrolyzed in the fermentation medium to rifamycin S. The enzymes from *Monocillium* spp. ATCC 20621 and *Humicola* spp. ATCC 20620 are intracellular (175,176) whereas the enzyme from *Curvularia lunata* var. *aeri* is extracellular (177). The use of a fluidized bed reactor containing immobilized whole cells of *Humicola* for the transformation of rifamycin B to rifamycin S has been described (178). Rifamycin SV producing strains have been isolated, but it is not known if these strains are used commercially.

Assay Methods. A large number of assays exist for the determination of the various rifamycins. Rifamycin SV and rifampicin can be determined by a microbiological assay using *Sarcina lutea* ATCC 9341 as the test organism (130,168), and rifampicin can be determined using *S. aureus* 560 (179). Rifamycins B, S, and SV can be separated by electrophoresis on agar gel and determined microbiologically using *B. subtilis* or *S. lutea* (180). Spectrophotometric assays exist for the rifamycins (130,168,181,182) and for rifampicin (183–185). Rifamycins B, O, S, and SV can be determined via polarography (186) or by amperometric titration (187). Rifamycins B, O, S, and SV can be separated by thin-layer chromatography on silica gel or by paper chromatography (188). Fluorimetric assays exist for rifamycin B (189) and rifampicin (179). High performance liquid chromatographic (hplc) procedures exist for rifamycins B, O, S, and SV (190), for rifampicin in formulations (191,192), in body fluids (193–197), in mixtures of antibiotics (198,199), and for rifapentine in plasma (200).

The *British Pharmacopoeia* specifies a biological assay for the sodium salt of rifamycin SV [14897-39-3]. It also specifies a spectrophotometric assay for rifampicin (201). The *United States Pharmacopeia* requires an hplc assay for rifampin (202).

Tolypomycins. The addition of small amounts of iron salts to the fermentation medium increases the production of tolypomycin Y (**48**) (7,203,204), the structure of which was arrived at by chemical degradation (205,206) and confirmed by x-ray crystallographic analysis (207) (Fig. 5). Mild acid hydrolysis of tolypomycin Y yields tolypomycinone [24356-23-6] (**49**, $R = H$), $C_{37}H_{43}NO_{13}$, and tolyposamine [34174-76-0], $C_{11}H_{13}NO_2$ (**50**). Further hydrolysis of tolypomycinone using acid yields tolyponone [24317-12-2] (**51**), $C_{14}H_{10}O_7$, which is also formed upon mild acid hydrolysis of rifamycin S. Reduction of tolypomycin Y produces tolypomycin R [33889-22-4] (**52**), $C_{43}H_{55}N_2O_{14}$ (208).

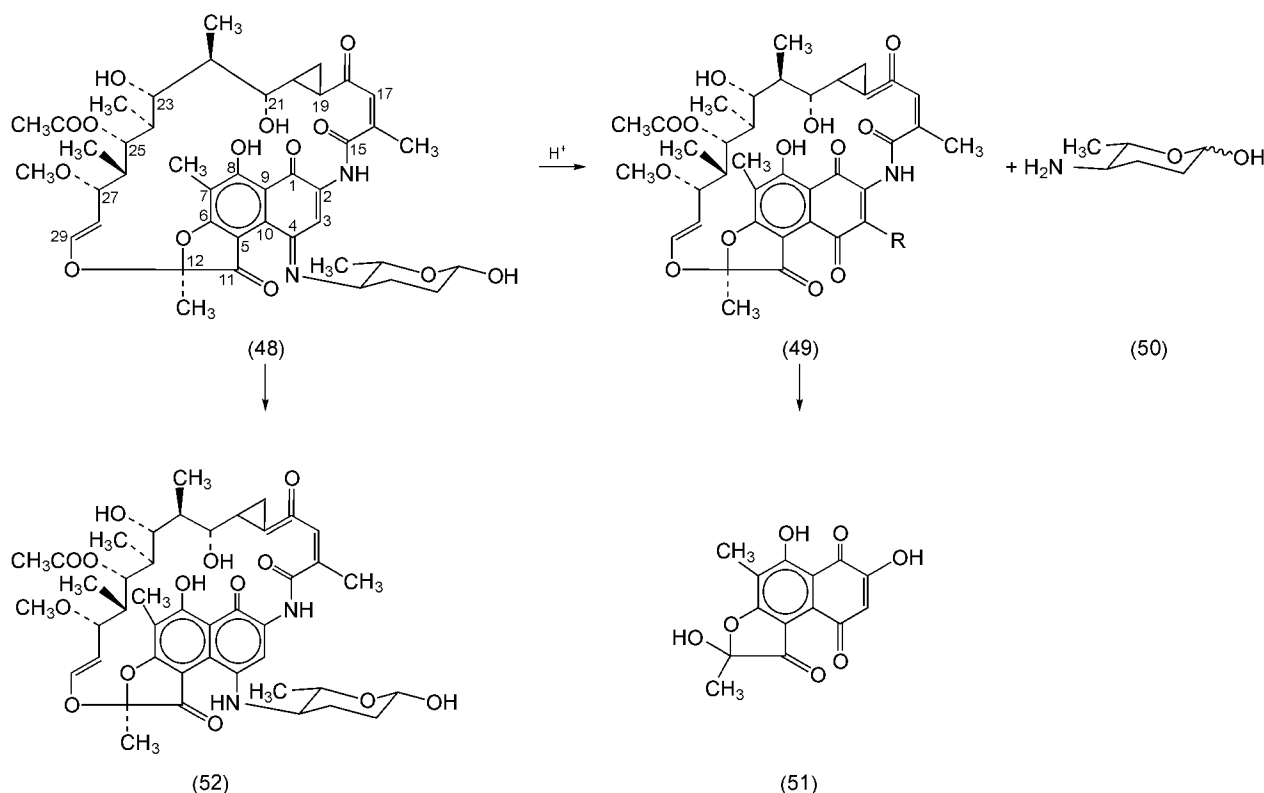


Fig. 5. Structures of the tolypomycins and degradation products.

Tolypomycin Y (**48**) shows strong antibacterial activity against gram-positive bacteria and *Neisseria gonorrhoeae*. When administered by subcutaneous, intraperitoneal, and intravenous routes, tolypomycin Y is effective in mice infected with *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Diplococcus pneumoniae*. Cross-resistance is observed with rifampicin but not with other antibiotics. Resistance to tolypomycin Y develops rapidly. The bioactivity of tolypomycin R

(52) is similar to that of tolypomycin Y (48) (208).
Tolypomycinone reacts with primary amines to form 3-*N*-substituted derivatives (209). The most interesting representative of this class of derivatives is 3-[β-(*N*-morpholy)ethylamino]tolypomycinone (M 045) [63793-73-7] (49, R = NHCH₂CH₂N(CH₂CH₂)₂O), C₄₃H₅₅N₃O₁₄, which has greater activity against gram-positive bacteria than tolypomycin Y, whereas its activity towards gram-negative bacteria is similar to that of rifampicin. Because of greater stability in acidic solution, M 045 has a greater therapeutic effect than tolypomycin Y in mice (210).
A differential bioassay was developed to distinguish tolypomycin Y from rifamycin B (211).
Halomycins. The halomycins are a group of four antibiotics produced by *Micromonospora halophytica* and separated by partition chromatography on Chromosorb W coated with formamide (19). Further purification was accomplished using preparative tlc (212).
Treatment of halomycin B (55) using nitrous acid yields rifamycin S (24) and the pyrrolidine (57) as shown in Figure 6. The halomycin B structure was confirmed by heating rifamycin O (23) and (57) in tetrahydrofuran to yield halomycin B (20) which can also be converted to rifamycin S by electrochemical oxidation (213). Upon treatment with nitrous acid, halomycin A (54) yields rifamycin S along with the pyrrolidine (58). The structure for halomycin C (56) was determined to be 20-hydroxy halomycin B based on mass spectral data (212).

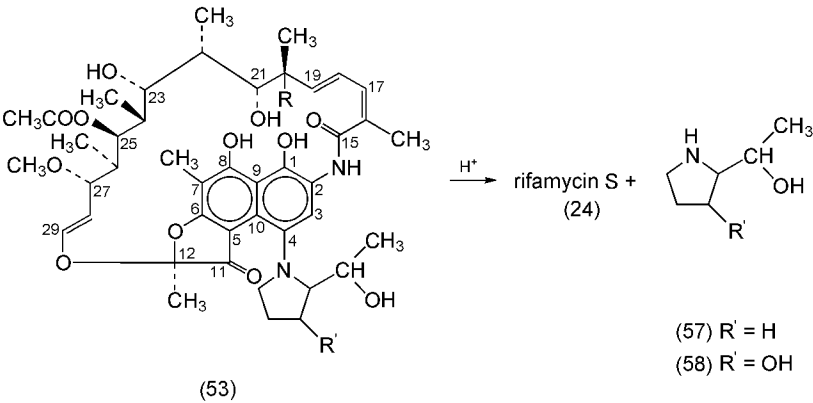


Fig. 6. Structures of the halomycins (53) and degradation products where for halomycin A (54) R = H, R' = OH; for halomycin B (55) R = R' = H; and for halomycin C (56) R = OH, R' = H.

The halomycins are active against gram-positive bacteria. The halomycin complex exhibited high activity against bacterial strains resistant to penicillin G. Halomycin C appears to be the most active component of the complex (19). X-ray crystallographic studies indicated that the pyrrolidine ring alters the conformation of the ansa-chain relative to rifamycin SV by changing the spatial arrangements of the C-21 and C-23 hydroxyl groups, which are important for biological activity against DNA-dependent RNA polymerase (214).
Naphthomycins, Naphthoquinomycins, Actamycin, and Diastovaricins. The naphthomycins, shown in Figure 7, are a group of closely related antibiotics differing in the substituent at C-2 and C-30, and in the geometry about the C-4 and C-6 double bonds. The naphthoquinomycins, diastovaricins, and actamycin are all closely related to the naphthomycins. Naphthomycin A (59) is isolated from a fermentation beer of *Streptomyces collinus* (*Tb 105*) (21). The structure originally proposed, based solely on nmr data, placed the phenolic group at C-27 rather than at C-25 as shown (215). However, spectral data for streptovaricin precursors and the reported value for the chemical shift of the phenolic proton, led to the proposal that the phenolic group was at C-25 (216). This was confirmed by degradation studies (217). Ozonolysis of (59) followed by treatment with diazomethane resulted in the isolation of (72) [72033-45-5], which, by reaction with sodium periodate, yielded (73) [72033-46-6] after treatment with diazomethane. The isolation of (72) and (73) confirmed the placement of the phenolic group at C-25. X-ray crystallographic studies confirmed the geometries assigned to the double bonds based on nmr studies and established the configuration as 8(*S*), 9(*S*), 15(*S*), 18(*S*), 19(*S*), and 20(*S*) (218). Naphthomycin A is active against gram-positive bacteria, but this activity is reversed by the addition of cysteine. It is also a vitamin K antagonist. Several sulfur-containing derivatives of naphthomycin A have been prepared (219) where the chlorine atom is replaced by an SR group. The biological activity of the C-3 *S*-substituted derivatives is similar to that of naphthomycin A.

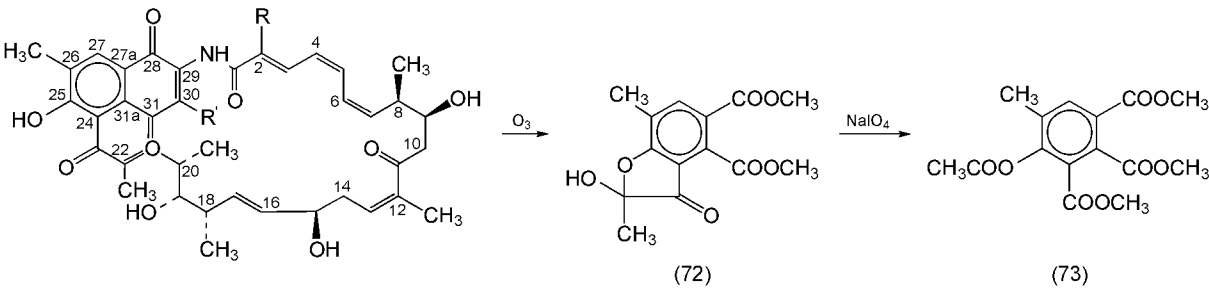


Fig. 7. Structures of the naphthomycins, naphthoquinomycins actamycins, and diastovaricins.

Ansamacrolide	Substituent		Double-bond geometry					
	R	R'	C-2	C-4	C-6	C-12	C-16	C-21
naphthomycin A (59)	CH ₃	Cl	Z	Z	E	E	E	E
naphthomycin B (60)	H	Cl	Z	E	Z	E	E	E
naphthomycin C (61)	H	H	Z	E	Z	E	E	E
naphthomycin D (62)	CH ₃	OH	Z	Z	E	E	E	E
naphthomycin E (63)	CH ₃	H	Z	Z	E	E	E	E
naphthomycin F (64)	CH ₃	SCH ₂ CH(NHCOCH ₃)COOCH ₃	Z	Z	E	E	E	E
naphthomycin G (65)	CH ₃	SCH ₂ CH(NHCOCH ₃)COOH	Z	Z	E	E	E	E
naphthomycin H (66)	H	Cl	Z	Z	E	E	E	E
naphthoquinomycin A (67)	H	OCH ₃	Z	Z	E	E	E	E
naphthoquinomycin B (68)	H	SCH ₃	Z	Z	E	E	E	E
actamycin (69)	H	OH	Z	Z	E	E	E	E
diastovaricin I (70)	H	OH	Z	E	Z	E	E	E

diastovaricin II (71)	H	SCH ₂ CH(NHCOCH ₃)COOH	Z	E	Z	E	E	E
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Naphthomycin B (60) is produced by *Streptomyces galbus* (Tb 353) whereas naphthomycin C (61) is produced by *Streptomyces diastatochromogenes* (Tb 1892) (220). The structures for (60) and (61) were arrived at on the basis of nmr data in comparison with those of (59). The antibacterial activity of naphthomycin B is similar to that of naphthomycin A. Naphthomycin C is nearly inactive against bacteria and fungi. Naphthomycins D (62), E (63), F (64), and G (65) are isolated from a fermentation beer of *Streptomyces aurantiogriseus* (Tb 2357) (221). Structures were determined by nmr and degradation studies using ozone. Naphthomycin F exhibits some activity against gram-positive bacteria and fungi while naphthomycins D, E, and G are biologically inactive. Naphthomycin H (66) is isolated from *Streptomyces* Y-83,40369 and was shown to be a geometrical isomer of naphthomycin B (222). The biological activity of naphthomycin H is similar to that of naphthomycins A and B.

Naphthoquinomycins A (67) and B (68) are isolated from *Streptomyces S-1998* (223) and the structures for (67) and (68) assigned on the basis of spectral data. Naphthoquinomycins A and B inhibit fatty acid synthesis in *E. coli*. Actamycin (69) is obtained from *Streptomyces* sp. E/784, and its structure arrived at on the basis of spectral data and degradation studies (224,225).

Diastovaricins I (70) and II (71) are produced by *Streptomyces diastochromogenes*. Diastovaricins I and II are active against Friend mouse leukemia cells. Spectral data were used to determine the structures (226).

Kanglemycin. Kanglemycin (74) (Fig. 8) is isolated from the fermentation broth filtrate of *Nocardia mediterranei* var *kangleensis* (1747-64) and its structure determined by x-ray crystallographic studies. The antibiotic is active against gram-positive bacteria (28).

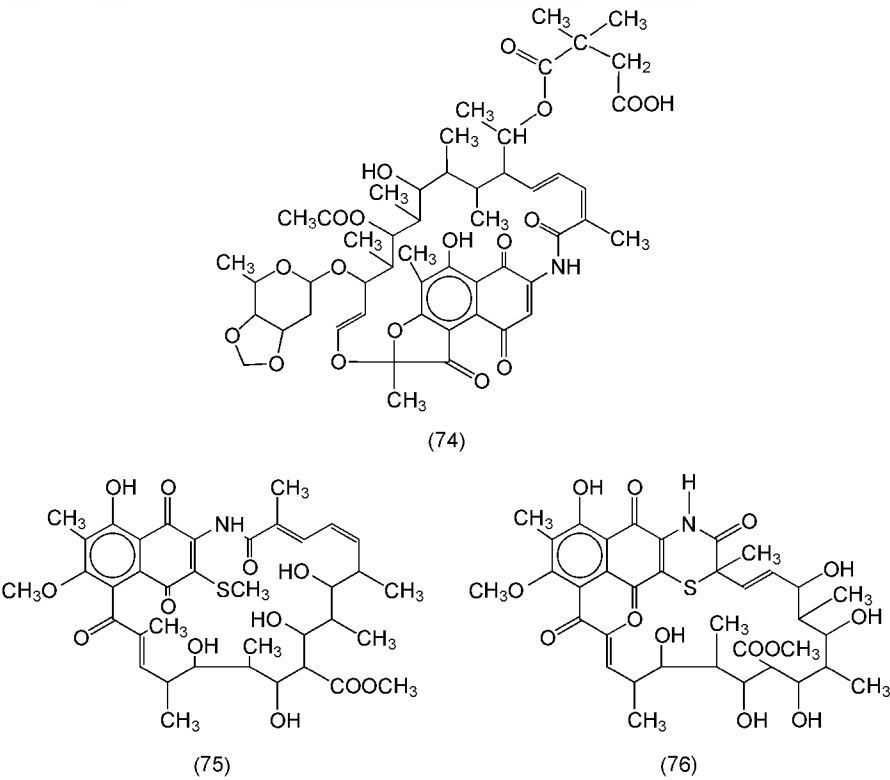


Fig. 8. Structures of kanglemycin (74), awamycin (75), and ansathiazin (76).

Awamycin and Ansathiazin. Awamycin (75) and ansathiazin (76) (Fig. 8) are produced by *Streptomyces albolongus* C-46366 (29); awamycin is also produced by *Streptomyces* sp. No. 80-217 (227). A mutant of *S. albolongus* (CM-11) formed by uv-mutagenesis produced 10 times more antibiotic than the parent strain. The structures for awamycin and ansathiazin were assigned on the basis of spectral data. Both antibiotics are active against gram-positive bacteria and awamycin is reported to have antitumor activity.

Benzoquinoids

Geldanamycin. Geldanamycin (77) (Fig. 9) is isolated from the filtered beer of *Streptomyces hygroscopicus* var. *geldanus* var. *nova* (30). This organism also produces nigericin, nocardamine, and a libanamycinlike activity depending on the composition of the fermentation medium (228). The structure of geldanamycin was assigned in great part on the basis of nmr studies (4,229). Unlike the naphthoquinoid ansamacrolides, geldanamycin has little antibacterial activity, being primarily active against protozoa and fungi, especially *Tetrahymena pyriformis* and *Crithidia fasciculata* (see ANTIPARASITIC AGENTS) (30). Geldanamycin also has herbicidal activity (see HERBICIDES) (230,231).

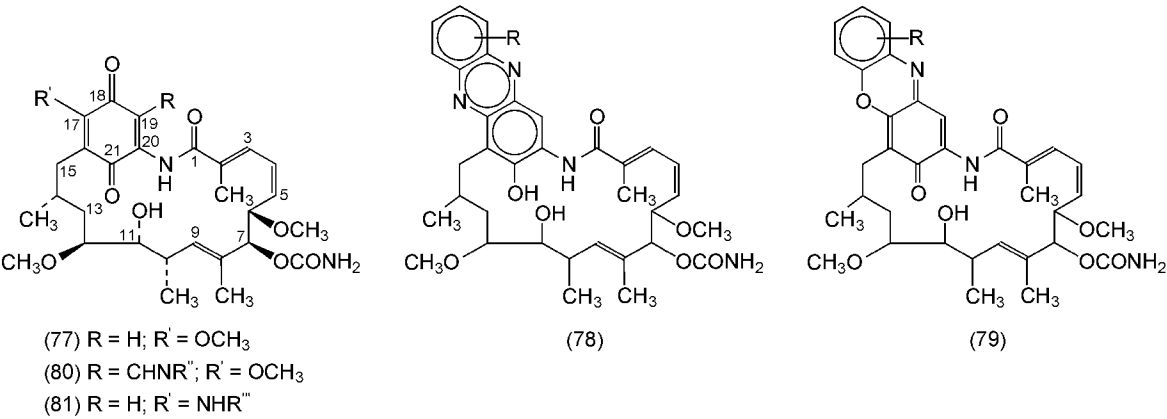


Fig. 9. Structures of geldanamycin (77) and derivatives.

Geldanamycin undergoes reaction with *o*-phenylenediamines and *o*-aminophenols to give compounds similar to rifazine (36, R = H). The corresponding geldanazines (78) and geldanoxazines (79) are active *in vitro* against reverse transcriptase but have no significant *in vivo* activity (232,233). Oxime and hydrazone derivatives of geldanaldehyde (80) similar to rifampicin (39) have been prepared and found to inhibit reverse transcriptase (234). Geldanamycin derivatives in which the 17-methoxy group has been replaced by a 17-alkylamino group (81) were found to have antitumor activity (235).

Herbimycins. Herbimycins A (82), B (83), and C (84), shown in Figure 10 along with some derivatives, are isolated from the fermentation broth of *Streptomyces hygroscopicus* AM-3672 (31). The structure of herbimycin A was assigned on the basis of spectral data (32) and confirmed by x-ray crystallographic studies (236). The structures for herbimycins B and C were derived by comparing spectral data to those for herbimycin A (34,35). The herbimycins possess strong herbicidal activity and exhibit some antitumor and antiviral activity.

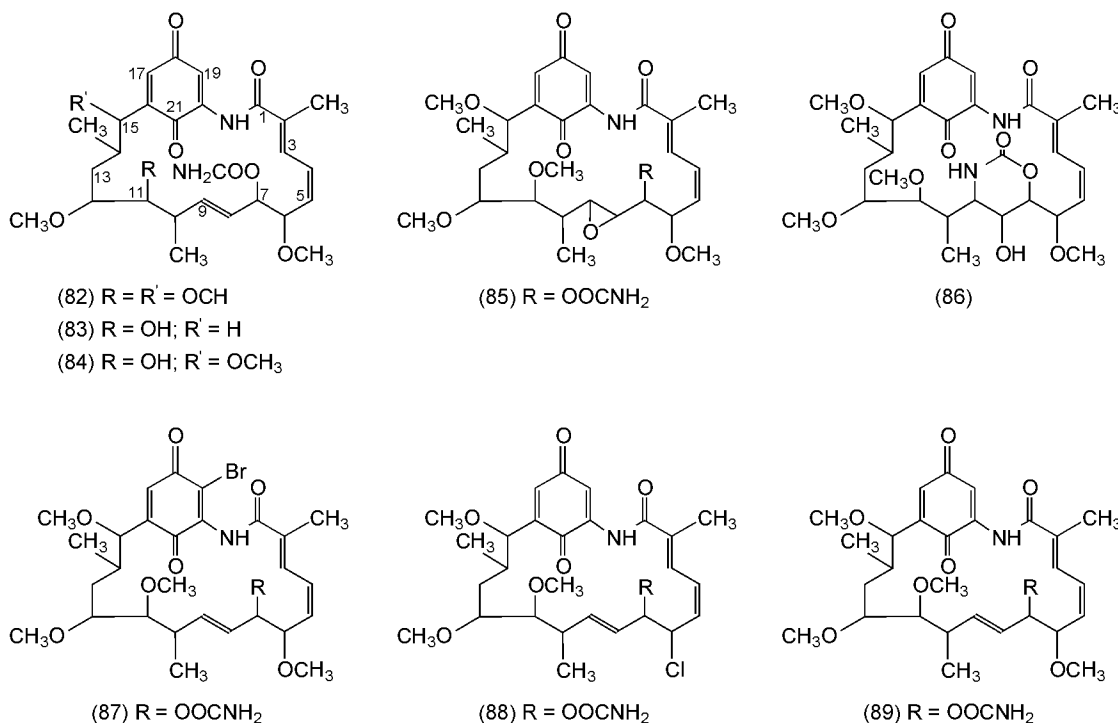


Fig. 10. Structures of the herbimycins and derivatives.

Several derivatives of herbimycin A have been prepared that possess greater antitumor activity than the parent. Treatment of herbimycin A with *m*-chloroperbenzoic acid yields 8,9-epoxyherbimycin A [94513-90-3] (85), C₃₀H₄₂N₂O₁₀, which upon treatment with boron trifluoride etherate is converted to herbimycin A-7,9-cyclic carbamate [94513-91-4] (86), C₃H₄₂N₂O₁₀. Treatment of (82), (85), or (86) with substituted amines yields the corresponding 17- or 19-amino derivatives. Most of the 19-amino derivatives examined, along with (85) and (86), have increased antitumor activity relative to herbimycin A (237). Other derivatives possessing antitumor activity include: 19-bromoherbimycin A [103224-24-4] (87), C₃₀H₄₁BrN₂O₉, which is formed by treating herbimycin A with pyridinium hydrobromide perbromide; 6-chloro-6-demethoxyherbimycin A [103224-10-8] (88), C₂₉H₃₉ClN₂O₈, which is formed by treating herbimycin A with boron trichloride; and, 2,3,4,5-tetrahydroherbimycin A [103224-30-2] (89), C₃₀H₄₄N₂O₉, formed by catalytic hydrogenation of herbimycin A (238).

Macbecins. Macbecin I (90) and II (91) (Fig. 11) are isolated from the fermentation broth of *Nocardia* sp. C-14919 (35,239). The structures were assigned on the basis of ¹H nmr studies on the intact antibiotics as well as on several degradation products. The assigned structures were confirmed by x-ray crystallographic studies (36). The macbecins are active against gram-positive bacteria, fungi, and protozoa and exhibit *in vitro* antitumor activity against murine leukemia P 388 and melanoma B 16 (35) (see CHEMOTHERAPEUTICS, ANTICANCER).

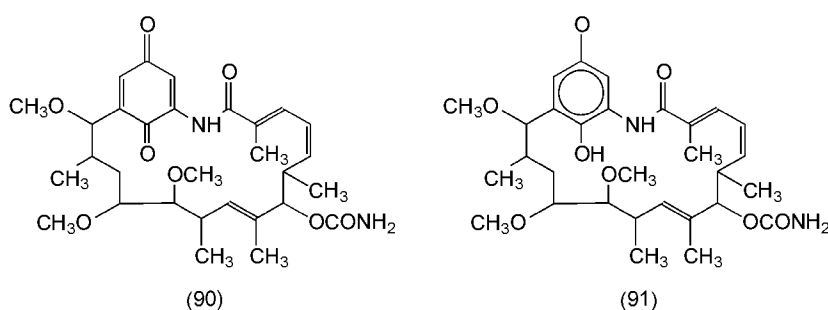


Fig. 11. Structures of macbecin I (90) and macbecin II (91).

Mycotrienins, Mycotrienols, Trienomycins, and Ansatrienins. The mycotrienins are produced by *Streptomyces rishiriensis* T-23 (38). The structures for mycotrienins I (92) and II (93) are shown in Figure 12. They were assigned primarily on the basis of nmr spectral analysis (37,240). Mycotrienins I and II are interconvertible via a redox reaction and acid hydrolysis of either compound yields D-alanine. Minor amounts of 20-O-methylmycotrienin II (94) and 23-de-oxymycotrienin II [97955-33-4], C₃H₅₀N₂O₇, which is identical to trienomycin A (97), are also isolated from the *Streptomyces rishiriensis* T-23 fermentation broth (41). The structures are also shown in Figure 12.

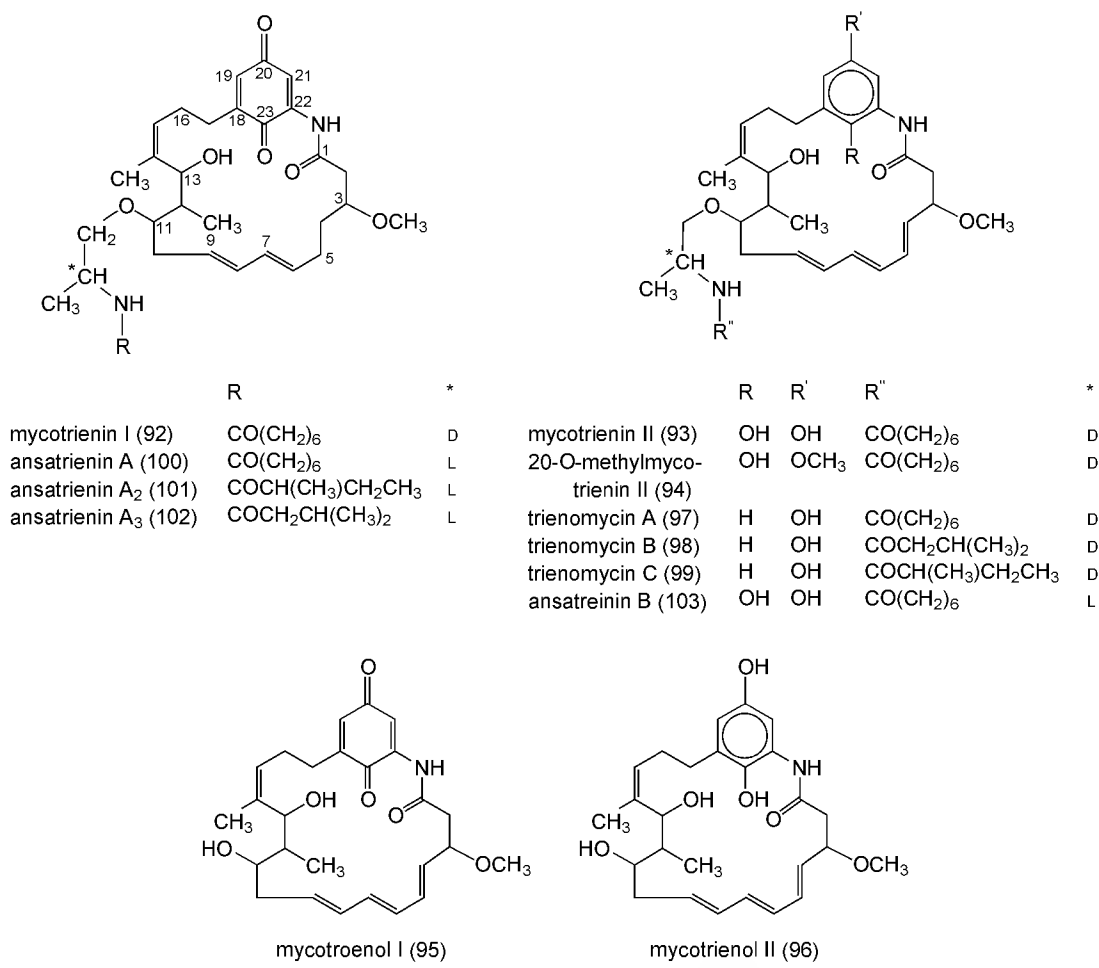


Fig. 12. Structures of the mycotrienins, mycotrienols, trienomycins, and ansatrienins where * represents configuration of the asymmetric center.

Streptomyces rishiriensis T-23 also produces mycotrienols I (95) and II (96), the structures of which were based on spectral analysis. Treatment of mycotrienin II (93) with lithium aluminum hydride yields a mixture of mycotrienols I and II (40). The mycotrienols are also interconvertible via a redox reaction. The mycotrienins possess no antibacterial activity but are active against fungi and yeasts (qv), and exhibit weak antitumor activity. The mycotrienols are an order of magnitude less active than the mycotrienins, suggesting that the cyclohexanecarbonylalanine group is important for biological activity.

The trienomycins are isolated from *Streptomyces* sp. 83-16 (43,44). The assigned structures (Fig. 12) were based on spectral data. Acid hydrolysis of trienomycin A yielded D-alanine (42,44). The trienomycins have no antimicrobial activity but have good antitumor activity. Trienomycin A is the most active, exhibiting good *in vivo* antitumor activity against sarcoma 180 and P 388 leukemia in mice (241).

The ansatrienins are produced by *Streptomyces collinus* T_b 1982. The structures (Fig. 12) were assigned on the basis of spectral data of the intact antibiotics as well as several derivatives. Acid hydrolysis of the ansatrienins yields L-alanine. The structures of ansatrienins A and B are the same as those for mycotrienins I and II, respectively, except for the configuration of the alanine moiety. The ansatrienins are active against fungi (45,46).

Maytansinoids and Maytansides (Ansamitocins).

Isolation and Structure Proof. The maytansinoids were the first ansamacrolides to be found in plants. The term "maytansinoids" refers to those ansamacrolides related to maytansine (104), shown in Figure 13, whereas the term "maytansides" refers to maytansinoids lacking the ester side chain at C-3 as well as the corresponding elimination products (50). Maytansine (104) was first isolated from the alcoholic extract of *Maytenus ovatus* Loes. (47). Several other maytansinoids and maytansides have been isolated from this species (Table 1). The structure of maytansine was established by x-ray crystallographic analysis (47,242), and the structures of the other maytansinoids and maytansides were arrived at by comparative nmr studies using maytansine (48–52). The absolute configuration of maytansine is 3(*S*), 4(*S*), 5(*S*), 6(*R*), 7(*S*), 10(*R*), and 2'(*S*). Maytanvaline (105) is converted to maysine (110) and *N*-isovaleryl-*N*-methyl-L-alanine by basic methanolysis. Basic methanolysis of maytansine (104) also yields maysine alone with *N*-acetyl-*N*-methyl-L-alanine. Normaysine (111) is converted to maysenine (112) by treatment with chromous chloride in acetic acid. Maytanbutine (107) and maytanacine (109) are converted to maytansinol (113) upon reduction with lithium aluminum hydride. Maytansinol can be converted to maytanacine by treatment with acetic anhydride–pyridine.

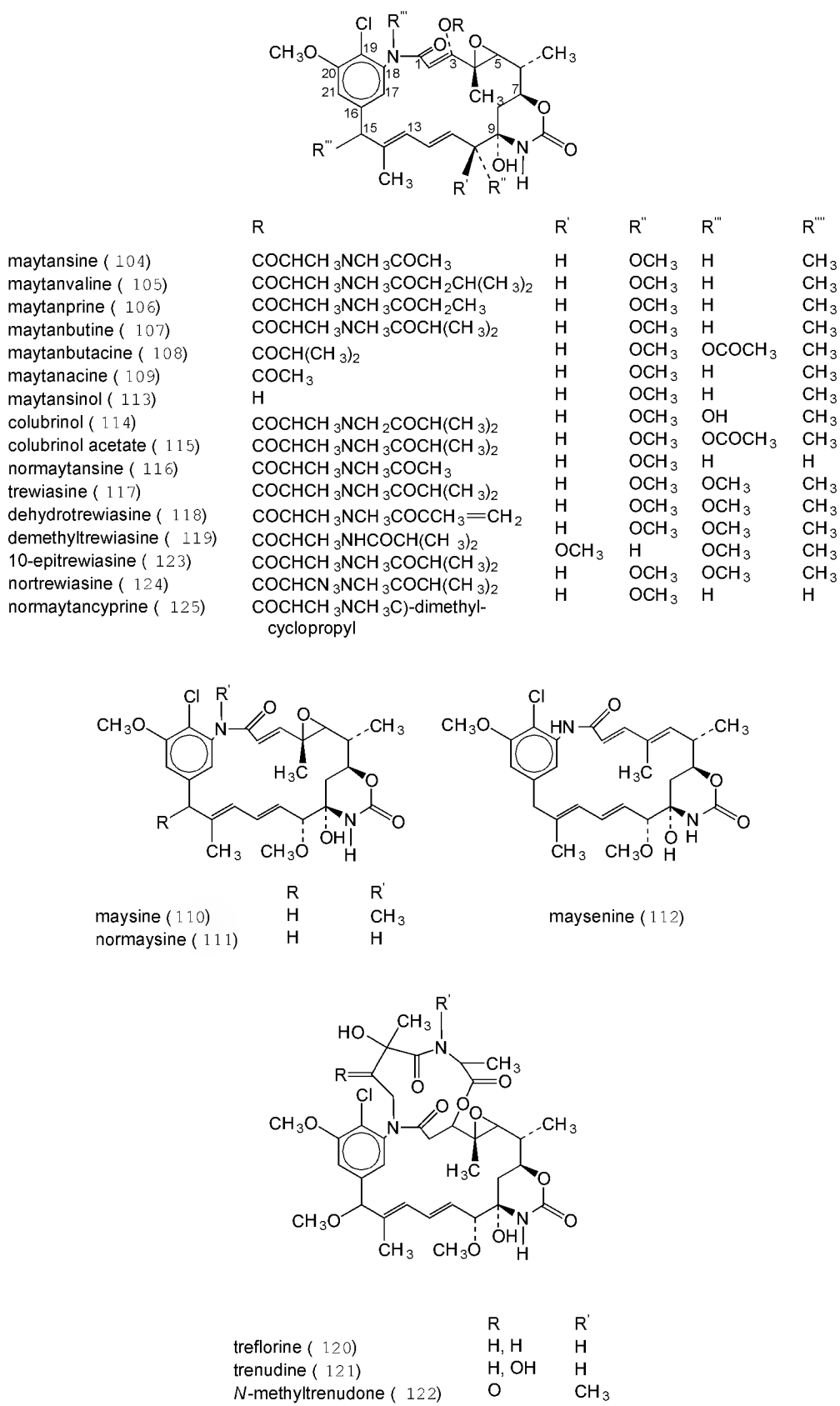


Fig. 13. Structures of the maytansinoids from plant sources.

Colubrinol (114) and colubrinol acetate (115) are isolated from *Colubrina texensis* Gray (*Rhamnaceae*) along with maytanbutine (51). Colubrinol is also isolated from *Trewia nudiflora* (*Euphorbiaceae*) (52). The structures for colubrinol and colubrinol acetate (Fig. 13) were established by high resolution ms and the comparison of their nmr spectra with that of the known maytanbutine.

Normaytansine (116) is isolated from *Maytenus buchananii* (54) and the maytansinoids trewiasine (117), dehydrotrewiasine (118), and demethyltrewiasine (119) are isolated from the ethanolic extract of the seed from *Trewia nudiflora* L. (*Euphorbiaceae*) (55). Also isolated from *Trewia nudiflora* are the maytansinoids treflorine (120), trenudine (121), and N-methyltrenudone (122), all of which contain an additional macrocyclic ring linking C-3 to the aromatic amide nitrogen (56). Several minor constituents were also isolated from the extract of *Trewia nudiflora* and include 10-epitrewiasine (123), nortrewiasine (124), and colubrinol (52). As with the other maytansinoids, these structures were elucidated by nmr and mass spectral studies. Normaytancyprine (125) is isolated along with maytansine from *Putterlickia verrucosa* Speggyl. (*Celastraceae*) (57).

Another large group of maytansinoids are produced by the microorganism *Nocardia* sp. C-25003 (N-1) and are designated ansamitocins (243). The structures of the ansamitocins, shown in Figure 14, were determined by spectral analysis. By comparison of reported physical data, it was concluded that ansamitocins P-0 (113), P-1 (109), and P-2 (126) were identical to maytansinol, maytanacine, and maytansinol propionate, respectively. Reductive cleavage of each ansamitocin yielded maytansinol. Alkaline hydrolysis of ansamitocins P-3 (127), P-3 (128), and P-4 (129) yielded isobutyric, butyric, and isovaleric acids, respectively.

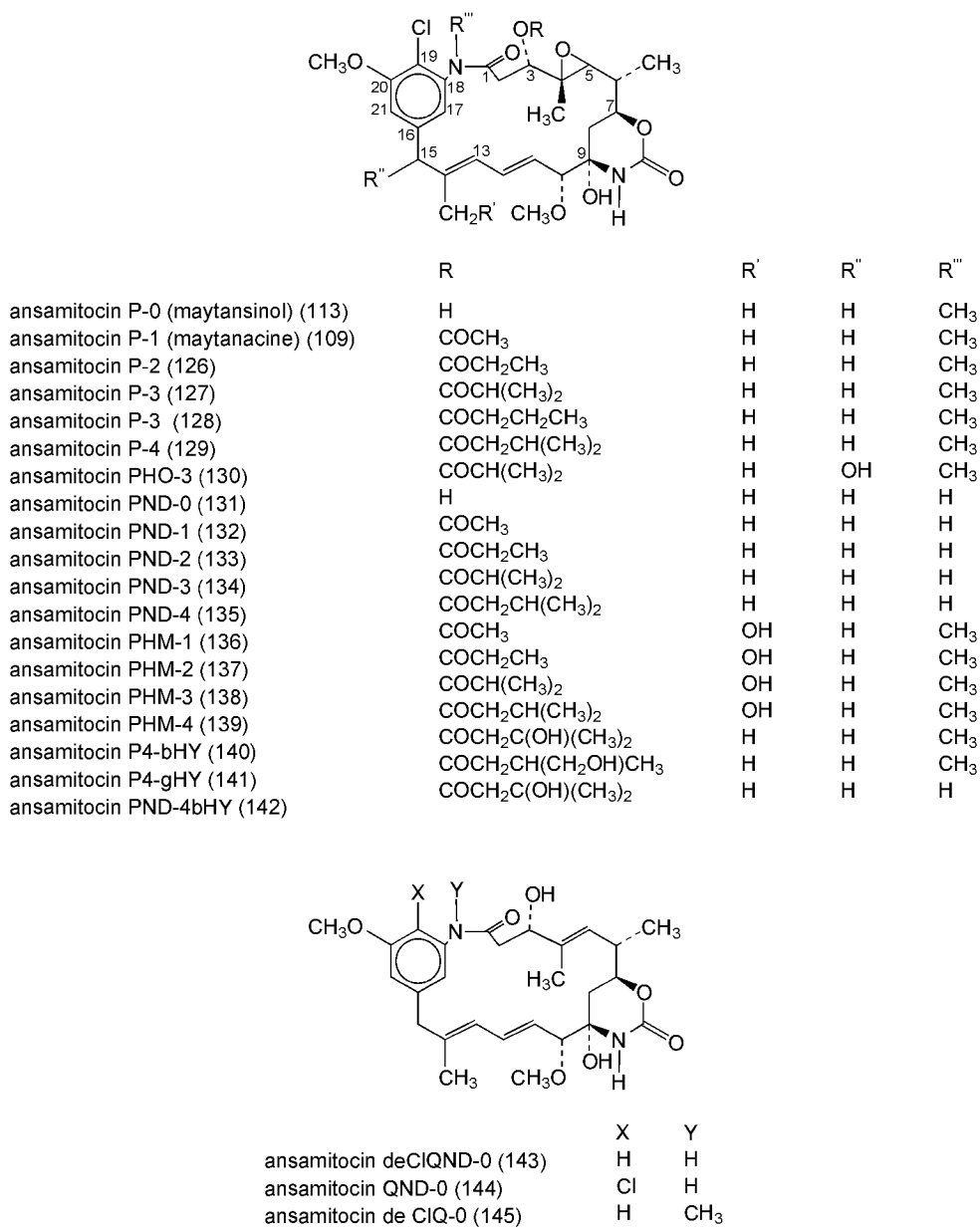


Fig. 14. Structures of the ansamitocins (maytansinoids from microorganisms).

A mutant of *Nocardia* sp. C-14482 (N-1001) was prepared by treatment with ethidium bromide to produce the strain N-1231 which subsequently produced ansamitocins P-3 and P-4 in high yield. This mutant also produces sixteen minor ansamitocins isolated following the scheme used for the parent strain. The structures of the newer ansamitocins were determined on the basis of spectroscopic evidence and were designated PHO-3 (130), PND-0 (131), PND-1 (132), PND-2 (133), PND-3 (134), PND-4 (135), PHM-1 (136), PHM-2 (137), PHM-3 (138), PHM-4 (139), P4-βHY (140), P4-γHY (141), PND-4βHY (142), deCIQND-0 (143), QND-0 (144), and deCIQ-0 (145) (59,244) (Fig. 14). There is speculation that microorganisms such as *Nocardia* may be involved in the production of maytansinoids in plants (243). Ansamitocin P-3 has been isolated from two thudiaceous mosses, *Cladpodium crispifolium* (Hook.) Ren. and Card. and *Anomodon attenuatus* (Hedw.) Hueb. (245).

Factors affecting the accumulation of ansamitocins P-2, P-3, and P-4 in *Nocardia* sp. C-15003 have been studied (246): the addition of isoleucine, propionate, propionaldehyde, or *n*-propyl alcohol to the fermentation medium resulted in the increased production of P-2; the addition of valine, isobutyrate, isobutyraldehyde, or isobutyl alcohol increased the production of P-3, reaching more than 90% of the total ansamitocins produced; and the addition of leucine, isovalerate, isovaleraldehyde, or isoamyl alcohol increased the production of P-4.

Large-scale isolation of maytansine (104), maytanprine (106), and maytanbutine (107) from the seeds of *Maytenus rothian* (Walp) Lobreau-Callen from India is possible using preparative lc. As much as 75 g of crude extract can be chromatographed to yield maytansinoids in gram quantities. *Maytenus rothian* is the best known source of maytansinoids (247). A preparative separation using hplc has also been developed for the ansamitocins, capable of handling 5 g of material per run. A quantitative hplc assay has also been developed to determine the amount of ansamitocins in the fermentation of beer (248).

Compilations of the physical properties of the maytansinoids are found in two reviews (249,250).

Chemical Properties and Derivatives. Procedures for the total synthesis of several of the maytansinoids have been thoroughly reviewed (249,250). A variety of bacteria, actinomycetes, yeasts, and fungi were screened for their ability to modify the ansamitocins. Four general types of transformations were performed by many of the strains examined, most of which were actinomycetes. *Bacillus megaterium* IFO 12108, *Streptomyces flavotricini* IFO 12770, and *Streptomyces platensis* IFO 12901 converted ansamitocins P-4, P-3, P-2, P-1, and P-0 to the corresponding 20-*O*-demethyl derivatives (designated PMD-4, PMD-3, PMD-2, PMD-1, and PMD-0, respectively). PMD-3 was found to have better antitumor activity against P 388 and L 1210 than P-3. Maytansine was also 20-*O*-demethylated by the two *Streptomyces* strains. *Streptomyces coelicolor* IFO 3807 and *Streptomyces galbus* IFO 13399 deacylated P-4, P-3, P-2, and P-1 to yield maytansinol (P-0). Maytansine was not deacylated by either organism. *Streptomyces castaneus* IFO 13670 converts P-4, P-3, P-2, and P-1 to the corresponding 15-hydroxylated derivatives (designated PHO-4, PHO-3, PHO-2, and PHO-1, respectively). Upon further study, it was discovered that ansamitocin P-3 was converted into two 15-hydroxyl derivatives designated PHO-3 and epi-PHO-3. The configuration at C-15 was established as (R) for PHO-3 and (S) for epi-PHO-3 by x-ray analysis. *Streptomyces minutiscleroticus* IFO 13361 converted P-4, P-3, P-2, P-1, and P-0 to the corresponding *N*-demethylated derivatives designated PND-4 (135), PND-3 (134) PND-2 (133), PND-1 (132), and PND-0 (131), respectively (251–253).

Several semisynthetic maytansinoids have been prepared by acylating the C-3 hydroxyl group of maytansinol. Some of these derivatives have antiprotozoal and antitumor activity similar to maytansine (104) and ansamitocin P-3 (127) (52,254). 3-Epimaytansinoids have been synthesized and were not biologically active (255).

Biological Activity. The maytansinoids possess antitumor activity, particularly against P 388 lymphocytic leukemia, B 16 melanocarcinoma, and Lewis lung carcinoma. A number of semisynthetic esters of maytansinol have been prepared and exhibit good antileukemic activity (52,255). The maytansides lack antitumor activity, indicating that the ester at C-3 is a requirement for activity (50,52). The carbinolamide also appears to be necessary for

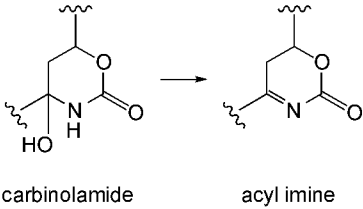
antitumor activity. The maytansinoids do not inhibit bacterial RNA polymerase as do the other ansamacrolides. Besides having antitumor activity, the ansamitocins have antiprotozoal and antifungal activity (243). Maytansine has undergone Phase I and II clinical studies and does not appear to be effective (249,250,256).

Mode of Action and Biosynthesis

The mode of action of the naphthoquinoid ansamacrolides was established through studies using the rifamycins and streptovaricins (84,141,257,258). The ansamacrolides inhibit bacterial growth by inhibiting RNA synthesis. This is accomplished by forming a tight complex with DNA-dependent RNA polymerase. This complex is between the ansamacrolide and the β-unit of RNA polymerase. The formation of the complex inhibits the initiation step of RNA synthesis (259,260). The ansamacrolides form no such complex with mammalian RNA polymerase and thus have low mammalian toxicity.

The antiviral activity of the ansamacrolides does not result from inhibition of RNA polymerase but rather from the inhibition of the assembly of the virus particles (141,258).

The antitumor activity of geldanamycin and its derivatives appears to result from inhibition of DNA synthesis whereas RNA synthesis is not affected (261). The antitumor activity of the maytansinoids also appears to result from the inhibition of DNA synthesis. The mechanism of action of maytansine (104) has been hypothesized to be the acid catalyzed loss of water from the C-9 hydroxyl group of the carbinolamide to form a reactive acyl imine intermediate, which reacts rapidly with nucleophiles on the bases of DNA (262).



The ansa-chain of the ansamycins streptovaricins (4), rifamycins (263), geldanamycin (4), and herbimycin (32) has been shown to be polyketide in origin, being made up of propionate and acetate units with the O-methyl groups coming from methionine. The remaining aromatic C₇N portion of the ansamacrolides is derived from 3-amino-5-hydroxybenzoic acid (264–266) which is formed via shikimate precursors. Based on the precursors of the rifamycins and streptovaricins isolated from mutant bacteria strains, a detailed scheme for the biosynthesis of most of the ansamacrolides has been proposed (95,263).

Commercially Available Ansamacrolides

Rifampicin, the only commercially available ansamacrolide, is manufactured by Merrell Dow under the tradename Rifadin, and by CIBA under the trade name Rimactane. Rifampicin is also supplied in combination with isoniazid or pyrazinamide [98-96-4]. The rifampicin–isoniazid combination is known as Rifamate (Merrell Dow), Rifinah (Merrell Dow), and Rimactazid (CIBA); the rifampicin–pyrazinamide as Rifater (Merrell Dow). Several other rifamycin derivatives including rifabutin and rifapentine are undergoing clinical studies.

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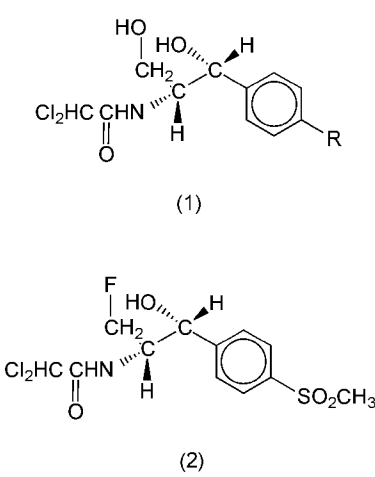
CHLORAMPHENICOL AND ANALOGUES

Chloramphenicol [56-76-7] (1, R = NO₂), C₁₁H₁₂Cl₂N₂O₅, is a commercially significant antibacterial agent and its status in clinical practice has been reviewed (1–6). Although widespread use of this antibiotic declined in the United States in the 1960s because of reports of serious toxic effects, this situation changed a decade later when ampicillin-resistant Hemophilus influenzae emerged on the clinical scene (3,6). The appearance of Bacteroides species and of Streptococcus pneumoniae (6) resistant to β-lactam antibiotics contributed further to the resurgence. In the 1970s, chloramphenicol also became important in the treatment of serious Salmonella invasive gastroenteritis in infants less than three months of age (5). Because chloramphenicol crosses the blood–brain barrier, it is indicated in infections of the central nervous system caused by susceptible organisms (5,7). The antibacterial activities of chloramphenicol and thiamphenicol [15318-45-3] (1, R = SO₂CH₃), C₁₂H₁₅Cl₂NO₅S, a close analogue, against a number of chloramphenicol-sensitive gram-positive and gram-negative organisms are given in Table 1.

Table 1. Minimum Inhibitory Concentration (MIC) of Chloramphenicol and Thiamphenicol Against Sensitive Organisms

Organism	MIC ^a , µg ml.	
	Chloramphenicol	Thiamphenicol
Enterobacter ridant	2	32
E. coli ATCC 10536	1	32
Klebsiella 0217604	4	64
Proteus mirabilis 12453	2	4
Proteus vulgaris Napolitano	2	32
Proteus rettgeri Hewitt 104	4	8
Serratia 0213605	16	> 128
B. subtilis 66333	2	4
Staphylococcus aureus 209P	4	8
Streptococcus pyogenes Bolden	4	4
Streptococcus 2040	4	4
Salmonella Gr. B. typhimurium	4	64
Shigella 1313	0.5	0.5

^a Agar dilution, 48 h, Mueller-Hinton agar.



The emergence of quinolones (see ANTIBACTERIAL AGENTS, SYNTHETIC) and other antibiotics is expected to curtail the use of chloramphenicol in the future, but this drug is relatively inexpensive, orally active, and the toxicity, except for the rare idiosyncratic aplastic anemia (1–6), can be managed through monitoring of blood levels by sensitive modern analytical procedures (3). However, clinical use is being further curtailed by the emergence of chloramphenicol-resistant organisms. In Table 2, the median *in vitro* susceptibilities of chloramphenicol, thiamphenicol, and a fluoroanalogue, florfenicol [76639-94-6] (2), C₁₂H₁₄Cl₂FNO₄S, against a host of chloramphenicol-sensitive and -resistant organisms are given. Bacteria resistant to chloramphenicol are also resistant to thiamphenicol.

Table 2. In Vitro Susceptibilities of Amphenicols

Organism strain	No. of strains tested	Susceptibility ^b	MIC, µg ml. ^a		
			Chloramphenicol	Thiomphenicol	Florfenicol ^c
Enterobacter	4	S	4	64	4
	14	R	512	1024	8
Citrobacter	3	S	4	32	8
	3	R	512	1024	128
E. coli	9	S	4	64	8
	20	R	256	1024	8
Klebsiella	9	S	4	64	8

	20	R	512	1024	4
<i>Providencia</i>	4	S	16	128	8
	12	R	128	1024	8
<i>Pseudomonas</i>	13	R	128	128	256
<i>Serratia</i>	6	S	16	512	64
	18	R	512	1024	64
<i>Salmonella</i>	15	S	4	32	8
	7	R	256	1024	8
<i>Shigella</i>	9	S	1	2	2
<i>Proteus</i>	23	R	256	512	8
<i>Acinetobacter</i>	4	R	64	512	128
	9	S	4	8	8
<i>Staphylococcus aureus</i>	7	R	64	512	8
<i>Streptococcus pneumoniae</i>	3	R	8	64	4

^a Agar dilution, 24 h, Mueller-Hinton agar.
^b S = susceptible; R = resistant.
^c Florfenicol data are from Ref. 8.

Both chloramphenicol and thiamphenicol cause reversible bone marrow suppression (9). The irreversible, often fatal, aplastic anemia, however, is only seen for chloramphenicol (9). This rare (1 in 10,000–45,000) chloramphenicol toxicity has been linked to the nitroaromatic function (1,9). Thiamphenicol, which is less toxic than chloramphenicol in regard to aplastic anemia, lacks potency as can be seen in Table 1, and thiamphenicol has never found much usage in the United States. An analogue of thiamphenicol having antimicrobial potencies equivalent to chloramphenicol was sought. Florfenicol (2) was selected for further development from a number of closely related structures.

Bacterial Resistance of Amphenicol

Of the many mechanisms of bacterial resistance to chloramphenicol and thiamphenicol, the plasmid-mediated transmissible resistance conferred by the presence in resistant bacteria of chloramphenicol-acetyltransferases (CAT) is the most important. This enzyme catalyzes the acetyl-CoA dependent acetylation of chloramphenicol and thiamphenicol (1,10–12). CAT is a cytoplasmic enzyme of which there are three main types: I, II, and III, type III being the most catalytically active (13). The most commonly observed variant of CAT appears to be type I, and type I and type III proteins are known to associate with one another to form hybrids possessing properties of both (13,14). The type III variant of CAT has been studied in detail by steady-state kinetics (13). The data indicate the formation of a ternary complex in the rate determining step involving the enzyme, acetyl-CoA, and chloramphenicol, but the tightness of substrate binding is not a contributing factor. Four types of CAT, type A, B, C, and D, have been characterized in *Staphylococcus aureus* (15) and type C seems to be the most common variant in this species.

Plasmid-mediated bacterial inactivation of chloramphenicol and thiamphenicol can potentially lead to three products, the 3-*O*-acetyl (3), 1-*O*-acetyl (4), and 1,3-di-*O*-acetyl (5) derivatives as shown in Figure 1.

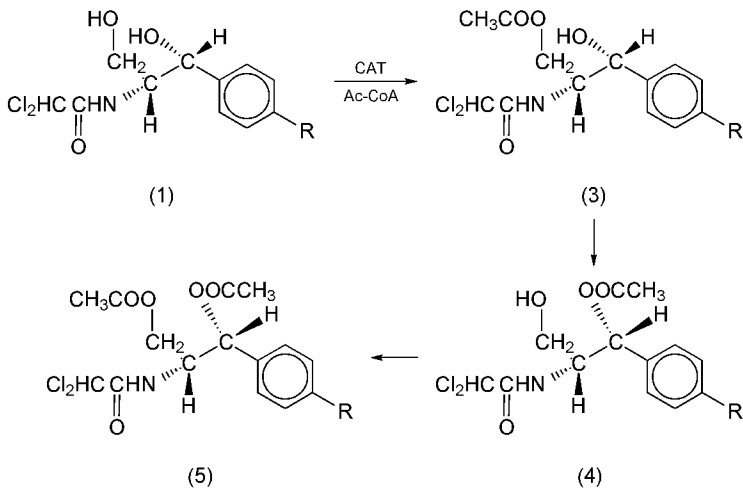


Fig. 1. CAT (catalyzed acetylation) of chloramphenicol (1, R = NO₂), and thiamphenicol (1, R = CH₃SO₂) where Ac-CoA is acetyl coenzyme A [72-89-9].

It was postulated (16–18) and later shown (10) that acetylation of the 3-hydroxyl group was the only enzymatic step in the inactivation process leading to products (3) and (5), and that formation of the 1-*O*-acetyl derivatives (4) resulted from a nonenzymatic intramolecular migration of the acetyl group from the 3- to the 1-position. Thus both the parent amphenicols (1) and the 1-*O*-acetyl derivatives (4) would seem to be substrates for the CAT enzyme (15,16,19) and prevention of enzymatic *O*-acetylation at the 3-position by replacement of that hydroxyl group using a suitable nonacylable function was proposed to block both modes of antibiotic inactivation (16). Extensive work on the modification of chloramphenicol at the 3-position had however, produced no therapeutically useful derivatives. Additionally, structure-activity relationship studies using chloramphenicol led to the conclusion that the 1,3-propanediol moiety was absolutely essential for amphenicol-type activity (20,21).

Structure-Activity Relationship of Chloramphenicol

Structure-activity and mechanism of action studies indicate that the requirements for chloramphenicol activity are: the D-threo-configuration, the 1,3-propanediol moiety, and a strong electron withdrawing group on the aromatic ring. The L-threo, the mirror image of (1), and the D-erythro and L-erythro isomers are not biologically active. Thus the speculation arose that certain specific intramolecular dipolar attractive interactions must exist in chloramphenicol leading to greater stabilization of one particular conformer over the others (16) where biological activity results from the most stable conformer.

The three basic conformational isomers of chloramphenicol are shown in Figure 2. In solution, the rotamers (a), (b), and (c) are expected to be in equilibrium and the concentration of any one of the three species at any given time is dependent on the nature of the solvent and temperature. Chloramphenicol has a specific rotation, [α]_D, of +18.5° in ethanol and –30° in dimethyl formamide (22).

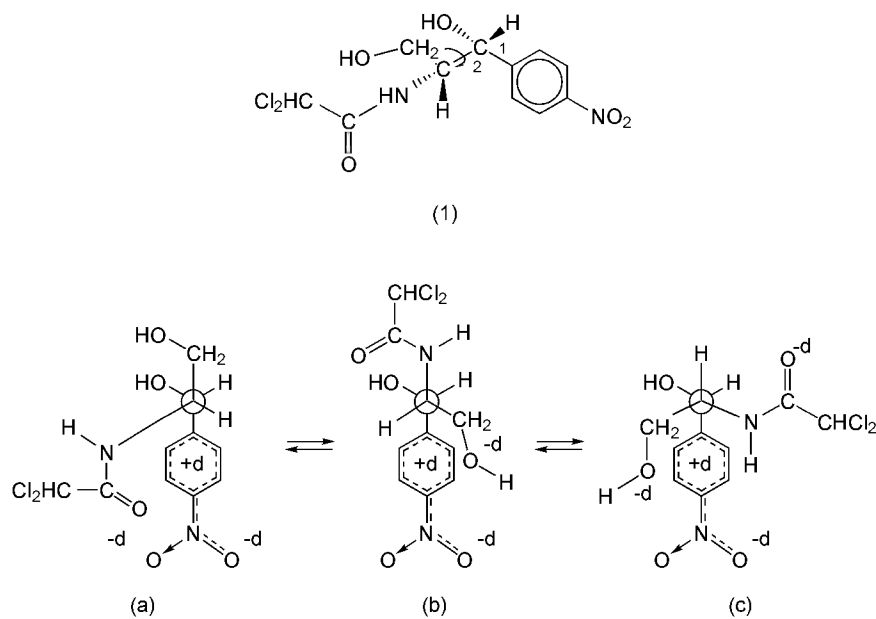
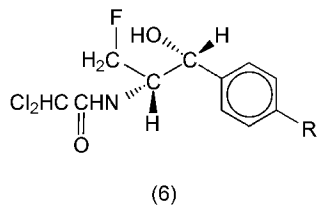


Fig. 2. Conformers (a), (b), and (c) of chloramphenicol (1, R = NO₂).

In solution, as in the crystalline state (23), the amide carbonyl bond is expected to be in a near syn-periplanar orientation with the C-2 hydrogen bond for all three rotameric forms (24–26). In the crystalline state, chloramphenicol exists in the rotameric form (a) (23) where the carbonyl group and the aromatic ring are in close proximity and the carbonyl atom is directed toward the π -electron system of the nitroaromatic ring suggesting strong dipolar attractive forces between the two moieties. In the rotameric form (b) such a dipolar interaction is not possible. Although, in conformer (c) a dipolar attractive interaction similar to the one seen in (a) is possible, it would require that the amide carbonyl bond depart from its thermodynamically preferred near syn-periplanar orientation to become near anti-periplanar. Therefore, rotamer (a) is the only conformation accommodating the preferred orientation of the amide carbonyl group with respect to both the C-2 methine hydrogen and the nitroaromatic group. Theoretical calculations (27) and molecular modeling (28) have also suggested that (a) is the most preferred conformation. Although the possibility of an intramolecular hydrogen bond between the 1,3 hydroxyl groups is implied in the x-ray crystal structure of chloramphenicol, the existence of such a bond in solution has been ruled out (27,29).

Fluoroanalogues

Because the lack of biological activity of 3-substituted chloramphenicols reported previously might result from the inability to exist in the "active" (a) type conformation, it was speculated that the size and nature of the C-3 substituent, maintenance of a low barrier to rotation about the C-2–C-3 bond, and the length of the carbon-substituent atom bond at C-3 were highly critical for achieving a conformational preference of the (a) type. Thus, on the basis of the van der Waals radii of fluorine and oxygen being the same (0.14 nm) and the average C–O and C–F bond lengths being close (0.131 nm, 0.138 nm, respectively), the C-3-hydroxyl group of chloramphenicol was replaced by a fluorine atom. Optical rotation measurements of 3-fluoro-chloramphenicol [73212-55-2], (6, R = NO₂), C₁₁H₁₁Cl₂FN₂O₄, in ethanol, gave $[\alpha]_D^{25} +24.4^\circ$ and in dimethylformamide gave -23.4° . Thus, as in the case of chloramphenicol, the optical rotation changed from a positive to a negative value on going from a protic to a dipolar aprotic solvent. The solid-state conformation was determined by single crystal x-ray structure analysis (30) and the crystals contained two rotameric structures in the asymmetric unit. The first conformer (Fig. 3a), corresponds to rotamer (a) of chloramphenicol where all the chloramphenicol conformational features are maintained. The other conformer, shown in Figure 3b, corresponds to the extended form (b) seen in Figure 2. The fluorine atom in this case is located close to the plane of the aromatic ring system supporting the explanation given for the stability of conformer (b) of chloramphenicol.



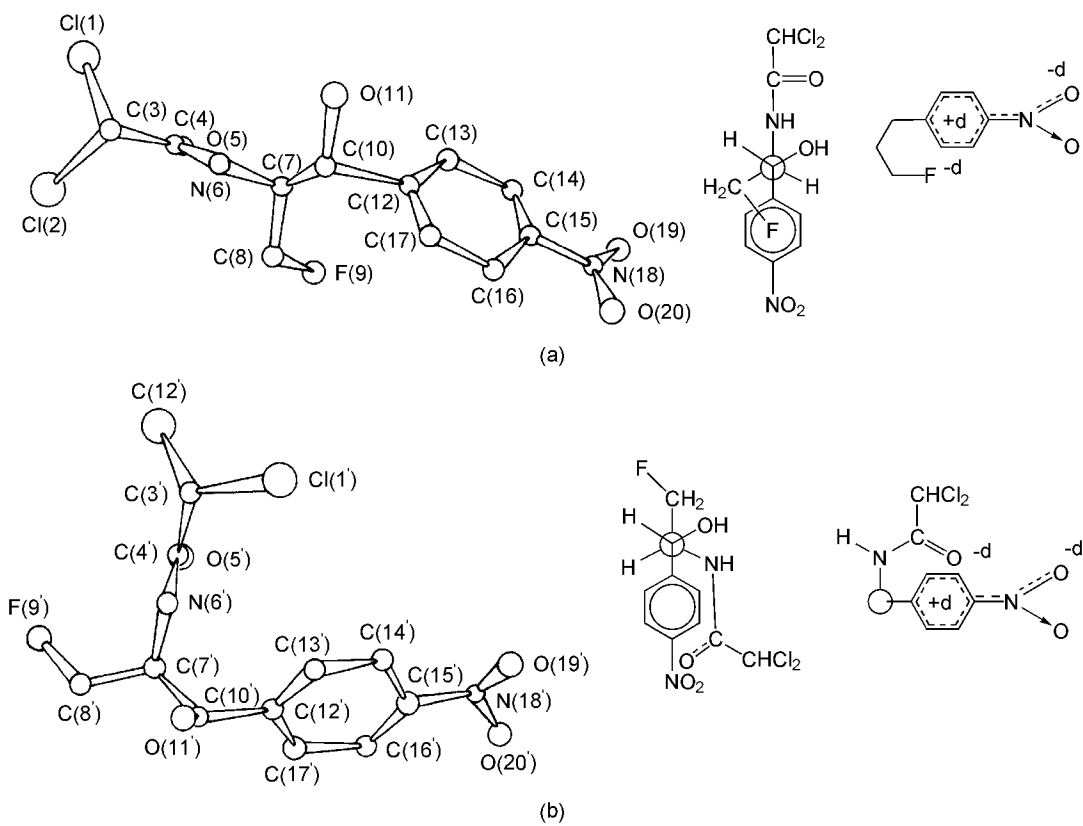


Fig. 3. The solid-state conformations of 3-fluoro-chloramphenicol (6, R = NO₂) showing the corresponding rotamers and schematics of the stabilizing attractive forces.

In solution, it is to be expected that rotamers (a) and (b) of structure (6) would exist in equilibrium with a third rotamer comparable to (c) of Figure 2, and that the thermodynamically preferred conformer (6a) would be responsible for biological activity. Removal of the nitro group from the aromatic ring was expected to have a destabilizing effect on the carbonyl-aromatic ring attraction in (6a) and in the solid state, the desnitro analogue (6, R = H) exists only in an extended form, comparable to rotamer (b), where the fluorine atom is no longer close to the plane of the aromatic ring. This desnitro compound is biologically inactive and it is therefore concluded that for activity a conformation of type (a) is required. The absence of the aromatic nitro group is thought to induce repulsive forces between the fluorine atom and the electron system resulting in the deflection of the fluorine away from the plane of the aromatic ring.

Biological Activity. The biological activity of 3-fluoro-chloramphenicol (6, R = NO₂) against chloramphenicol-sensitive and -resistant organisms was determined and is given in Table 3. Potencies against sensitive strains are similar to those of chloramphenicol. Additionally, this fluoroderivative is highly active against chloramphenicol-resistant organisms having MICs ranging from 1 to 16 µg/L. This result prompted the synthesis and biological evaluation of a number of amphenicols containing a fluorine atom at the 3-position. The activity of the most promising, florfenicol (2), 3-fluorothiamphenicol, is also given in Table 3. Florfenicol is not only active against the chloramphenicol-thiamphenicol-resistant strains, but the potency of florfenicol against sensitive organisms is also superior to any of the other amphenicols.

Table 3. Activity of Chloramphenicol and Analogues Against Chloramphenicol-Sensitive and -Resistant Organisms

Organism	MIC, µg mL ^a			
	Chloramphenicol	Thiamphenicol	3-Fluoro-chloramphenicol	Florfenicol
<i>Ent. aerogenes</i> Ridant	2	8	4	0.5
<i>Ent. aerogenes</i> Jackson	>128	>128	8	4
<i>E. coli</i> ATCC 10536	1	32	0.5	0.5
<i>E. coli</i> 0128604	>128	>128	16	16
<i>Kleb. pneumoniae</i> 0217604	4	64	8	8
<i>Kleb. pneumoniae</i> 1117501	>128	>128	2	2
<i>Prov. stuartii</i> Rahal	16	64	2	1
<i>Prov. stuartii</i> 4GR	>128	>128	16	2
<i>Serr. marcescens</i> 0213605	8	>128	8	8
<i>Serr. marcescens</i> Brooke 4	>128	>128	4	2
<i>Staph. aureus</i> 209P	4	4	4	0.5
<i>Staph. aureus</i> Ziegler	8	4	4	0.5
<i>Staph. aureus</i> 59N	4	4	1	0.5
<i>Staph. aureus</i> 1613	2	4	2	0.25
<i>Strep. pyogenes</i> Bolden	0.5	4	2	0
<i>Strep. pyogenes</i> Cruz	2		4	4
<i>Salm. Gr. B. typhimurium</i>	2	32	4	4
<i>Salm. Gr. C2 Newport</i>	2	8	4	2
<i>Shig. dysenteriae</i> ATCC 13213	0.5	0.25	0.25	0.25
<i>Shig. dysenteriae</i> SS1NO1	0.25	0.25	0.25	0.25
<i>Prot. mirabilis</i> ATCC 12453	4	1	4	1
<i>Prot. mirabilis</i> ATCC 12453	4	1	4	1
<i>Prot. morgani</i> Daly	8	32	8	1
<i>Prot. mirabilis</i> Charlot. Va.	32	32	8	0.5
<i>Prot. morgani</i> Garro	128	32	4	1
<i>Prot. rettgeri</i> 120	128	>128	16	2

^a Mueller-Hinton broth, 24 h.

The antimicrobial properties of florfenicol have been evaluated by several laboratories (8,31). As seen in Table 2, the median MICs of florfenicol against chloramphenicol-susceptible strains of *Enterobacter*, *Citrobacter*, *Providenia*, *Serratia*, *Salmonella*, and *Shigella* are similar to chloramphenicol whereas against *Klebsiella* the median MIC is half. However, against sensitive *Staphylococci* florfenicol is twice as potent as chloramphenicol. Thiamphenicol is considerably less potent than florfenicol against all of the above strains. Against 103 resistant strains, the MICs of chloramphenicol and thiamphenicol ranged from 64 to 1,026 µg mL. Mean values were 256 and 512 µg mL, respectively. For florfenicol, the MICs ranged from 1 to 64 µg mL against the same resistant organism; the median value was 8 µg mL.

Florfenicol inhibited 91° of the 399 bacterial isolates at a concentration of 12.5 µg mL (31). At the same concentration, chloramphenicol and thiamphenicol inhibited only 70° and 24° of the isolates, respectively. Other work has also confirmed the superior activity of florfenicol against chloramphenicol-resistant strains (32–35). More recently it has been shown that florfenicol is active against *E. coli* strains that produce type I, II, or III CAT enzymes (36).

Veterinary Potential or Florfenicol. The absolute ban on the use of chloramphenicol in food producing animals in the United States and Canada has accentuated the need for an effective broad spectrum antibiotic in animal food medicine. Florfenicol and other antibiotics commonly used in veterinary medicine have been evaluated *in vitro* against a variety of important veterinary and aquaculture pathogens. Some of these data are shown in Tables 4 and 5, respectively. Florfenicol was broadly active having MICs lower than those of chloramphenicol in each of the genera tested (Table 4). Florfenicol was also superior to chloramphenicol, thiamphenicol, oxytetracycline [79-57-2], ampicillin [69-53-4], and oxolinic acid [14698-29-4] against the most commonly isolated bacterial pathogen of fish in Japan (Table 5) (37).

Table 4. Activity of Florfenicol (2) and Chloramphenicol (1, R NO₂) Against Veterinary Bacterial Pathogens

Organism	No. of strains tested	MIC ₉₀ ^a (µg mL)	
		Florfenicol	Chloramphenicol
<i>Streptococcus spp.</i>	81	4.0	8.0
<i>Staphylococcus spp.</i>	23	5.0	64.0
<i>Staphylococcus spp.</i>	57	8.0	16.0
<i>Corynebacterium spp.</i>	14	2.0	16.0
<i>Clostridium spp.</i>	21	8.0	4.0
<i>Pasteurella multocida</i>	32	1.0	16.0
<i>E. coli</i>	272	16.0	>128.0
<i>Salmonella spp.</i>	68	16.0	>128.0
<i>Klebsiella spp.</i>	54	32.0	>128.0
<i>Proteus spp.</i>	26	16.0	>128.0
<i>Pseudomonas spp.</i>	35	>128.0	>128.0

^a MIC₉₀ is the antibiotic concentration at which 90° of the bacteria tested are inhibited.

Table 5. Minimum Inhibitory Concentrations (MIC₉₀^a) of Florfenicol (2) and Other Antibiotics Against Bacterial Pathogens Isolated from Fish in Japan, µg/mL

Antibiotic	Organism (No. of strains tested)		
	<i>Pasteurella piscicida</i> (50)	<i>Edwardsiella tarda</i> (50)	<i>Vibrio anguillarum</i> (35)
florfenicol	0.4	0.8	0.8
chloramphenicol	12.5	50.0	25.0
thiamphenicol	>100.0	>100.0	>100.0
oxytetracycline	6.3	50.3	
ampicillin	100.0		
oxolinic acid		1.6	

^a MIC₉₀ is the antibiotic concentration at which 90° of the bacteria tested are inhibited.

Florfenicol (2) has been approved in Japan for the treatment of pseudo-tuberculosis caused by *Pasteurella piscicida* and *streptococcosis* in yellowtail fish. The recommended dose is 10 mg kg for up to one week and the drug withdrawal time is five days after cessation of treatment. Florfenicol is active in bovine respiratory disease caused by *Pasteurella* species and mastitis caused by *Staphylococci* and *Streptococci*. It is also effective in neonatal colibacillosis caused by *E. coli*. The drug is being developed worldwide by Schering-Plough Animal Health for the treatment of aquatic and bovine diseases.

Structure–Activity Relationships of 3-Fluoro-amphenicols. A number of analogues of 3-fluorochloramphenicol (6, R NO₂) and florfenicol (2) have been synthesized and the biological activities examined. Replacement of the dichloroacetyl group by a difluoroacetyl function in both series led basically to retention of potency and the spectrum of activity of the parent structures. However, changing the difluoroacetyl to a trifluoro- or a chlorodifluoroacetyl group abolished the antimicrobial activity almost completely. Reduced level of potency was also seen when the dichloroacetyl group was changed to a chlorofluoroacetyl group. Other amide functions such as methoxyacetyl or methylsulfonylacetyl did not give any appreciable activity. In the florfenicol structure, changing the methylsulfonyl group to methylsulfoxide greatly reduced the potency and the methylthio analogue was practically inactive.

Mechanism of Action of Florfenicol. The inhibitory activities of chloramphenicol (1, R NO₂), thiamphenicol (1, R SO₂CH₃), and florfenicol (2) against a sensitive *E. coli* strain have been studied (36). In two different liquid media, both chloramphenicol and florfenicol allowed only 20–30° residual growth at a drug concentration of 2 mg L, whereas a thiamphenicol concentration of 25 mg L was required to produce a similar effect. Florfenicol was also found to be a selective inhibitor of prokaryotic cells. At concentrations of 1 mg L chloramphenicol and florfenicol, and at a concentration of 25 mg L, thiamphenicol, inhibited protein synthesis. Florfenicol inhibited peptidyl transferase selectively on 70S ribosomes and florfenicol, like chloramphenicol and thiamphenicol, was inactive against *E. coli* strain A19-CM which is resistant at the ribosome level. The binding site for the three amphenicols on the prokaryotic 70S ribosome is different from that on the eukaryotic 80S ribosomes which accounts for the observed selective action. Both chloramphenicol and thiamphenicol have a higher affinity than florfenicol for a common ribosomal-receptor site that represents the peptidyl transferase domain. Although florfenicol is the most potent of these three drugs as an inhibitor in a cell-free transcription system, it is least effective in inhibiting the puromycin [53-79-2] reaction which is a measure of inhibition of puromycin-induced release of ribosome-associated nascent peptides.

In Vivo Effects of Florfenicol. Comparative acute toxicities of florfenicol, chloramphenicol, and thiamphenicol in mice are given in Table 6. As can be seen, florfenicol is similar to thiamphenicol in acute toxicity by oral and subcutaneous (sc) administration, but is comparable to chloramphenicol by intraperitoneal (ip) and intravenous (iv) routes. Serum levels in mice following either a single or subcutaneous dose of 200 mg kg of amphenicol have

been determined and the results are given in Figure 4. The serum drug levels attained following oral administration were similar to those obtained by parenteral administration for all compounds. Serum levels of chloramphenicol and thiamphenicol were generally similar whereas florfenicol levels were much higher.

Table 6. Comparative Toxicities in Mice for Amphenicols

Compound	Route of Administration ^a			
	Oral	Ip	Sc	Iv ^b
chloramphenicol	2000	700	2450	90
thiamphenicol	>3000	>2500	>3000	370
florfenicol	>3000	1500	3000	100

^a The vehicle employed, unless otherwise noted, was 50% propylene glycol plus 50% of a biological vehicle where complete solubility of the drugs was not attained at the concentrations employed.

^b The vehicle employed was 25% propylene glycol plus 75% water and complete solubility was attained at the indicated concentrations.

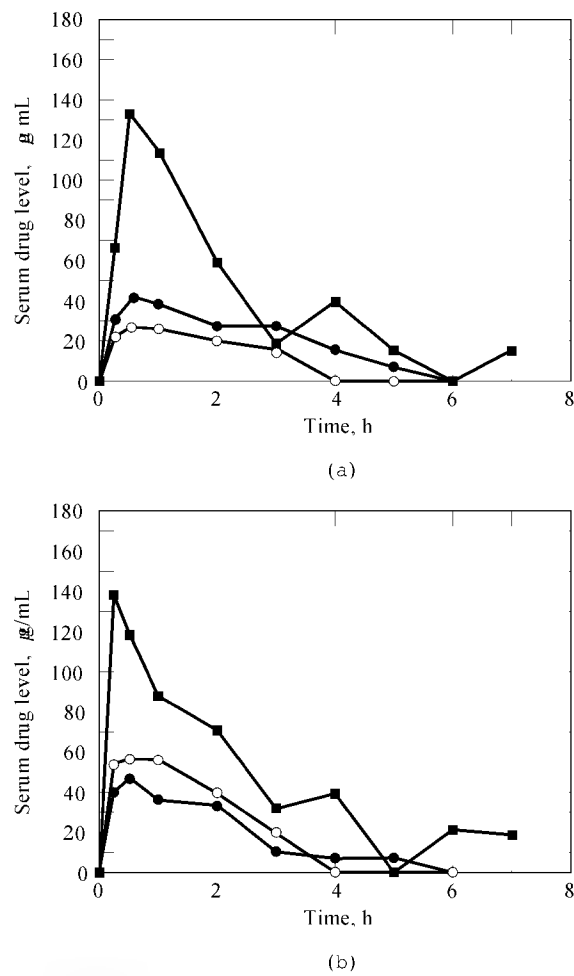


Fig. 4. Serum levels in mice of chloramphenicol (1, R NO₂) ●, thiamphenicol (1, R CH₃SO₂) ○, and florfenicol (2) ■, following a single dose of 200 mg kg given (a) subcutaneously, and (b) orally.

In rats, the observed serum drug levels were generally much lower than those seen at the same dose in mice which would seem to indicate a greater metabolic degradation of these compounds in rats. Once again, levels after oral administration were very similar to those given parenterally for all of the compounds. Serum levels attained using florfenicol were similar to those seen using thiamphenicol, however, these levels were lower after parenteral administration than after oral administration. Binding of florfenicol to serum protein is substantially higher than thiamphenicol binding at 60% and 16%, respectively, but is similar to chloramphenicol binding which is 47%.

The efficacy of florfenicol *in vivo* was determined by measuring the dose required to obtain values for protection from infection in 50% of the animals (PD₅₀) against 10 chloramphenicol-resistant strains and two chloramphenicol-sensitive isolates. Florfenicol, chloramphenicol, and thiamphenicol were evaluated concurrently against each strain. Against sensitive *Enterobacter*, PD₅₀ by the subcutaneous and oral routes were similar for florfenicol and chloramphenicol (25 mg kg sc, 5 mg kg oral), but higher for thiamphenicol (30 mg kg sc, 20 mg kg oral). A dramatic effect was seen for florfenicol against *Shigella* (3 mg kg sc, 2 mg kg oral) as compared to chloramphenicol and thiamphenicol (100 mg kg by both routes). Against resistant strains of *Enterobacter*, *Klebsiella*, *Providencia*, *Serratia*, *Salmonella*, and *Staphylococcus*, the PD₅₀ values for florfenicol ranged from 5 to 60 mg kg whereas chloramphenicol and thiamphenicol were practically ineffective.

Pharmacokinetics in Nonrodents

The pharmacokinetic disposition of florfenicol (2) was studied in preruminant veal calves after administration of a single 22 mg kg dose intravenously, orally after a 12-h fast, and orally 5 min postfeeding. The disposition of florfenicol in veal calves following a single iv dose was adequately described by a two-compartment open model where there was no significant effect of the animal's age on the pharmacokinetic parameters. Calves given the oral doses had a complex absorption pattern and delayed absorption. Administering florfenicol with milk delayed the onset of absorption and therefore the time to peak concentration. The disposition of the serum concentration of florfenicol in veal calves given by either oral method could be adequately described by a one-compartment pharmacokinetic model with first-order drug absorption and first-order drug elimination (38). The bioavailability of florfenicol was significantly less when given with milk replacer than when given on an empty stomach: after a 12-h fast median bioavailability was 88% of the dose; and

given 5 min postfeeding, median bioavailability of the drug was 65%.

The elimination half-life of florfenicol after a single iv dose of 22 mg/kg (138–204 min) compares well with the elimination half-life of chloramphenicol (1, R = NO₂) reported in cattle, except in very young calves. Half-lives of 350 min (39) and 302 min (40) in 1-week-old calves, 207 min (40) in 4-week-old calves, 210 min in 6-week-old calves (40), and 264 min (39) and 210 min (41) in adult cows have been reported. The apparent volume of distribution (V_d) for florfenicol following iv administration ranged from 0.68 to 0.84 L/kg as compared to V_d values following iv administration of chloramphenicol in calves of from 0.905 to 1.23 L/kg (39,40). The total body clearance (CL) for florfenicol, 2.77–4.00 mL/(kg·min), is also similar to the CL of chloramphenicol, 1.9–4.03 mL/(kg·min), in calves (39,40).

Florfenicol concentrations in tissues and body fluids of male veal calves were studied after 11 mg/kg intramuscular doses administered at 12-h intervals (42). Concentrations of florfenicol in the lungs, heart, skeletal muscle, synovia, spleen, pancreas, large intestine, and small intestine were similar to the corresponding serum concentrations indicating excellent penetration of florfenicol into these tissues. Because the florfenicol concentration in these tissues decreased over time as did the corresponding serum concentrations, it was deemed that florfenicol equilibrated rapidly between these tissues and the blood. Thus serum concentrations of florfenicol can be used as an indicator of drug concentrations in these tissues.

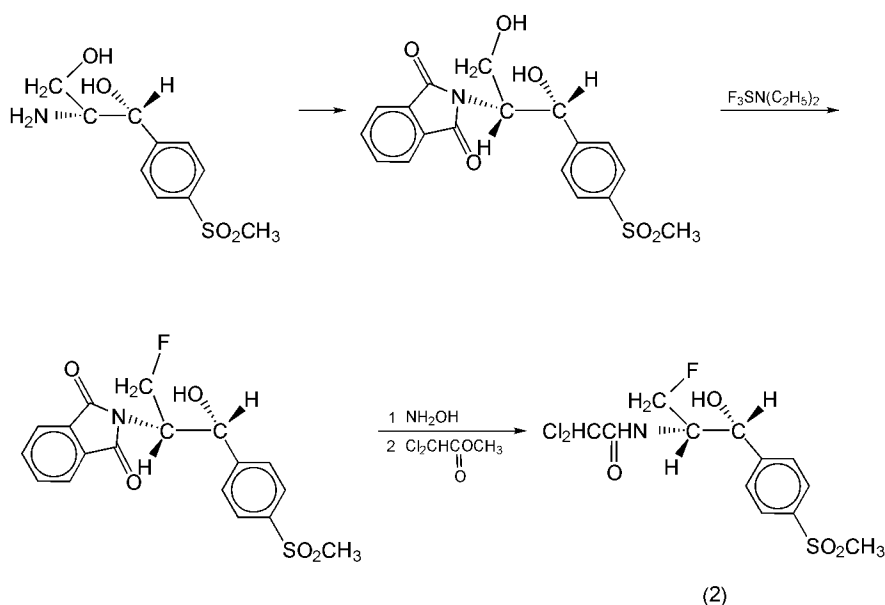
High florfenicol concentrations were found in the kidney, urine, bile, and small intestine of three calves and in the large intestine of one calf. High florfenicol concentrations in the kidneys and urine indicate that florfenicol may be an excellent drug for treating urinary tract infection caused by susceptible organisms. On the basis of the high concentrations of florfenicol in the bile and the good absorption of the drug after oral administration, florfenicol may undergo some degree of enterohepatic recirculation.

Florfenicol concentrations in the brain, cerebrospinal fluid (CSF), and aqueous humor were one-fourth to one-half the corresponding serum concentrations. Concentrations in these tissues and fluids did not decrease as rapidly, maintaining a low, but fairly constant value. Because the brain, CSF, and aqueous humor are separated from the blood by specialized barriers, florfenicol can seemingly only cross these barriers to a limited extent.

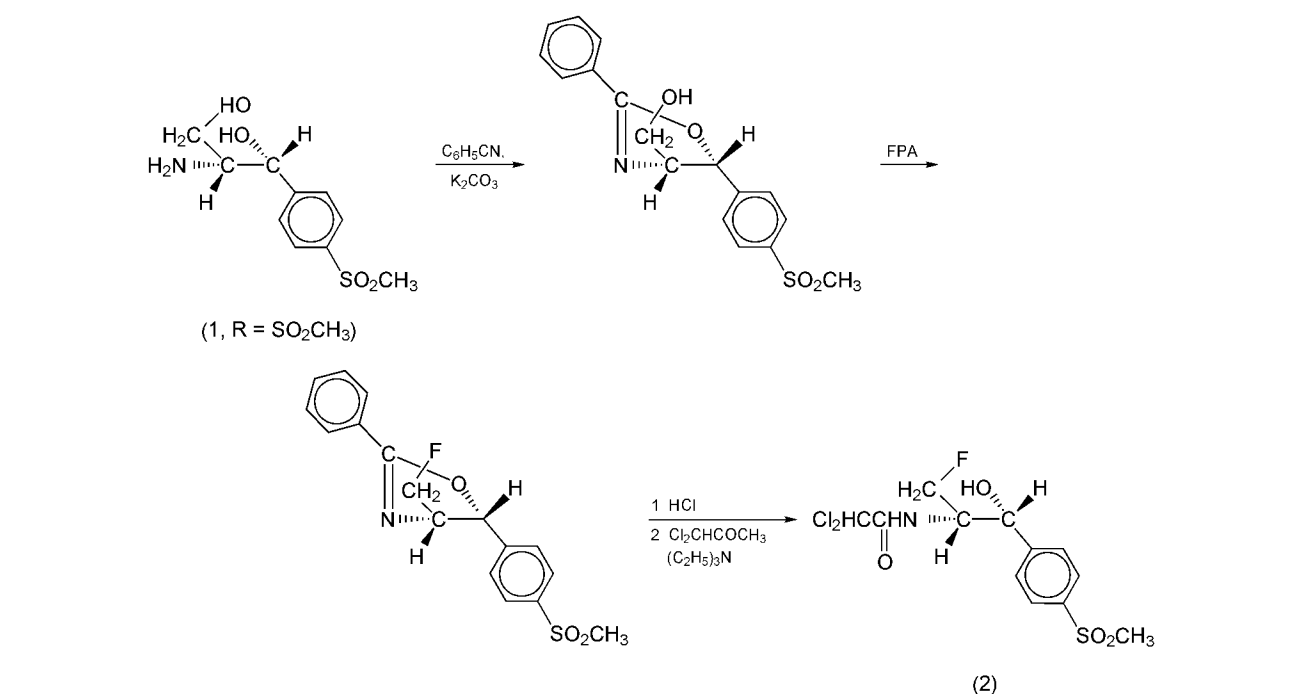
Florfenicol has a wide tissue distribution, similar to that reported for chloramphenicol in calves and thiamphenicol in humans (43,44). Chloramphenicol attains concentrations higher than the corresponding plasma concentrations in bile and urine, as does florfenicol (43). Unlike florfenicol, chloramphenicol concentrations in the liver, kidney, spleen, and lungs are less than corresponding plasma concentrations. However, chloramphenicol penetrates the brain and CSF much better than does florfenicol, reaching values equal to plasma concentrations in the brain. The distribution of thiamphenicol into the kidney, urine, and muscles of humans compared with corresponding plasma concentration is similar to what was observed for florfenicol in calves (44). The penetration of thiamphenicol into the CSF is much smaller than that of florfenicol in calves.

Synthesis

The first syntheses of florfenicol (2), 3-fluorochloramphenicol, (6, R = NO₂) and other fluoroanalogues were accomplished beginning with thiamphenicol (1, R = SO₂CH₃) according to the reaction sequence



(16,22). Because the starting materials were optically active, the products were all pure enantiomers. Later, the synthetic scheme shown in Figure 5 was developed (22,45). Resolution of the racemic mixture was accomplished at the penultimate stage and the optically active D-threo-amine (7) was converted to florfenicol (2). This synthetic process also resulted in the synthesis of thiamphenicol shown in Figure 6 using 1,1,2,3,3,3-hexafluoropropyl diethylamine (FPA) (46). More recently an improved method of synthesis of florfenicol has been developed (17).



The C—H bond of the dichloroacetyl group in chloramphenicol is readily oxidized by liver enzymes and the resulting oxalylchloride derivative is presumed to be implicated in chloramphenicol's toxic manifestation (48). Because such an oxidative mechanism might also be operative in bacterial systems, leading to inactivation of the antibacterial activity, the C—H bond was replaced by deuterium exchange under mildly basic conditions, in both the amphenicol and the 3-fluoroamphenicol series, to see if the rate of oxidation might be retarded. The deuterio analogues have been observed to be consistently twice as potent as the hydrogen analogues (49).

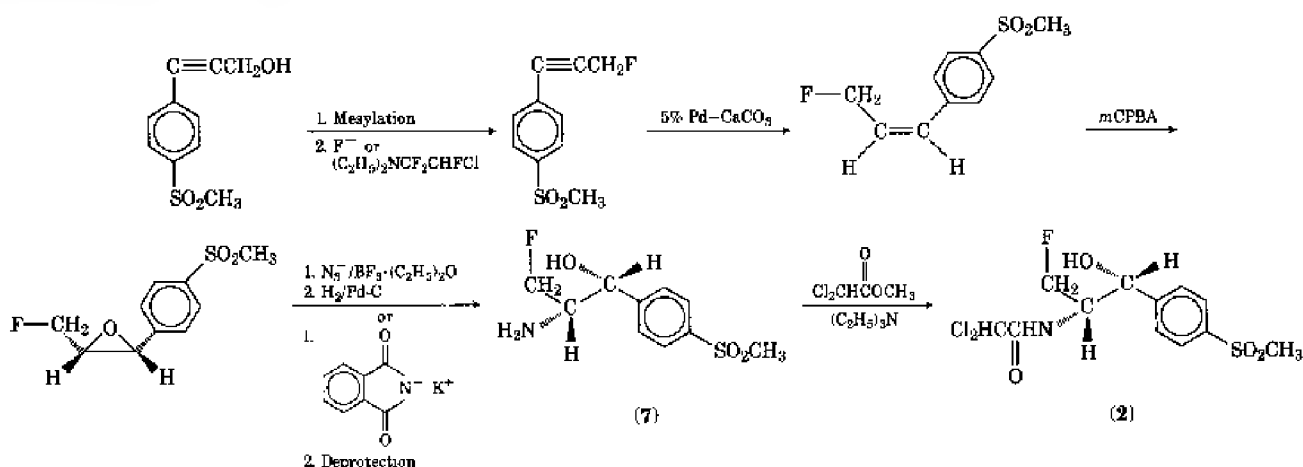


Fig. 5. Alternative synthesis of florfenicol (2) where *m*CPBA is *m*-chloroperbenzoic acid.

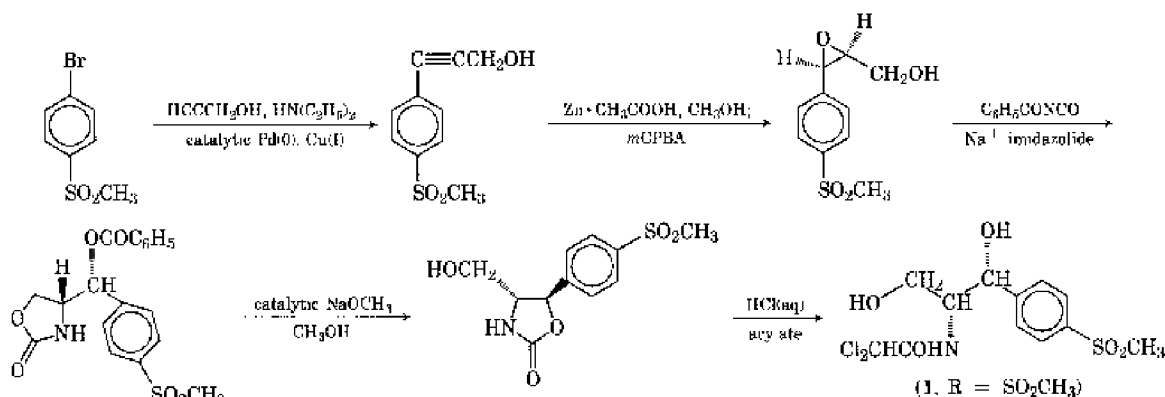


Fig. 6. Synthesis of thiamphenicol (1, R = SO₂CH₃) (47) where *m*CPBA is *m*-chloroperbenzoic acid.

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ELFAMYCINS

The elfamycins are so named because they exhibit antimicrobial activity through the inhibition of protein biosynthesis via binding to the *elongation factor* Tu (1). All of the known elfamycins are listed in Table 1 and the structures are given in Figure 1. These antibiotics are distinguished by low mammalian toxicity, narrow-range antimicrobial activity, and positive effects on feed utilization and growth promotion in farm animals. Elfamycins also improve milk production in lactating ruminants.

Table 1. Elfamycins

Antibiotic	CAS Registry Number	Molecular formula	Producing organism	Structure no.	Refs.
aurodox	[12704-90-4 /	C ₄₄ H ₂ N ₂ O ₁₂	<i>Streptomyces goldiniensis</i> var. <i>goldiniensis</i>	(1, R = CH ₃)	2–4
kirromycin ^a	[50935-71-2 /	C ₄₃ H ₀ N ₂ O ₁₂	<i>S. collinus</i> Tb 365	(1, R = H)	3,5–7
azdimycin	[57035-45-7 /	unknown	<i>S. diastatochromogenes</i> ATCC 31013		8
efrotomycin	[56592-32-6 /	C ₅₉ H ₈₈ N ₂ O ₂₀	<i>S. lactamdurans</i> NRRL 3802	(2, R = CH ₃)	9–13
dihydromocimycin	[61994-74-9 /	C ₄₃ H ₂ N ₂ O ₁₂	<i>S. ramocissimus</i> CBS190.69 CBS190.69	(3)	12,14
heneicomycin	[66170-37-4 /	C ₄₄ H ₂ N ₂ O ₁₁	<i>S. filipinensis</i> NRRL 11044	(4, R = CH ₃ , R' = C ₂ H ₅ , R'' = CH ₃)	12,15,16
kirrothricin	[79190-00-4 /	C ₄₄ H ₄ N ₂ O ₁₀	<i>S. cinnamomeus</i> Tb 89	(5)	12,17,18
factumycin	[84600-89-5 /	C ₄₄ H ₂ N ₂ O ₁₀	<i>S. lavendulae</i> ATCC 31312	(6)	12,19
MSD A63A	[81209-82-7 /	unknown	<i>Streptoverticillum hiroshimense</i>		20
L681,217	[93522-10-2 /	C ₃ H ₅₃ N ₁ O ₁₀	<i>S. cattleya</i> ATCC 39203	(7)	12,21,22
SB22484, factor 3	[97328-80-8 /	C ₄₁ H ₅ N ₂ O ₁₁	<i>S. strain</i> NRRL 15496	(4, R = H, R' = CH ₃ , R'' = H)	12,23,24
SB22484, factor 4	[97328-81-9 /	C ₄₂ H ₈ N ₂ O ₁₁	<i>S. strain</i> NRRL 15496	(4, R = H, R' = C ₂ H ₅ , R'' = H)	12,23,24
phenelfamycin A	[118498-91-2] 15	C ₅₁ H ₇₁ N ₁ O ₁₅	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(8, R = H, R' = COCH ₂ C H ₅)	12,25,26
phenelfamycin B	[118498-91-3] 15	C ₁ H ₇₁ N ₁ O ₁₅	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(8, R = COCH ₂ C H ₅ , R' = H)	12,26,27
phenelfamycin C	[118498-91-4] 18	C ₅₈ H ₈₃ N ₁ O ₁₈	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(9, R = H, R' = COCH ₂ C H ₅)	(12,26,27) 7)
phenelfamycin D	[118498-91-5] 18	C ₅₈ H ₈₃ N ₁ O ₁₈	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(9, R = COCH ₂ C H ₅ , R' = H)	12,26,27
phenelfamycin E	[114451-31-9] 21	C ₅ H ₉₅ N ₁ O ₂₁	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(10, R = H, R' = COCH ₂ C H ₅)	12,26,27
phenelfamycin F	[114451-30-8] 21	C ₅ H ₉₅ N ₁ O ₂₁	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(10, R = COCH ₂ C H ₅ , R' = H)	12,26,27
unphenelfamycin	[118117-42-3] 14	C ₄₃ H ₅ N ₁ O ₁₄	<i>S. violaceoniger</i> str. AB999F-80, AB1047T-33	(8, R = R' = H)	12,26,27
LL-E19020α	[114451-31-9] 21	C ₅ H ₉₅ N ₁ O ₂₁	<i>S. hydicus</i> sp. <i>tanzanius</i> NRRL 18036	(11, R = H, R' = COCH ₂ C H ₅)	28–32
LL-E19020β	[114451-30-8] 21	C ₅ H ₉₅ N ₁ O ₂₁	<i>S. hydicus</i> sp. <i>tanzanius</i> NRRL 18036	(11, R = COCH ₂ C H ₅ , R' = H)	28–32
UK-69,753	[118117-42-3] 18	C ₅₈ H ₈ N ₂ O ₁₈	<i>Amycolatopsis orientalis</i> ATCC 53550	(12)	12,31,33, 34
N-demethylefrotomycin	[124846-41-9] 20	C ₅₈ H ₈ N ₂ O ₂₀	<i>Nocardia</i> ATCC 53758	(2, R = H)	35

^a Identical to mocimycin which was isolated from *S. ramocissimus* CB5190.69 (6,36).

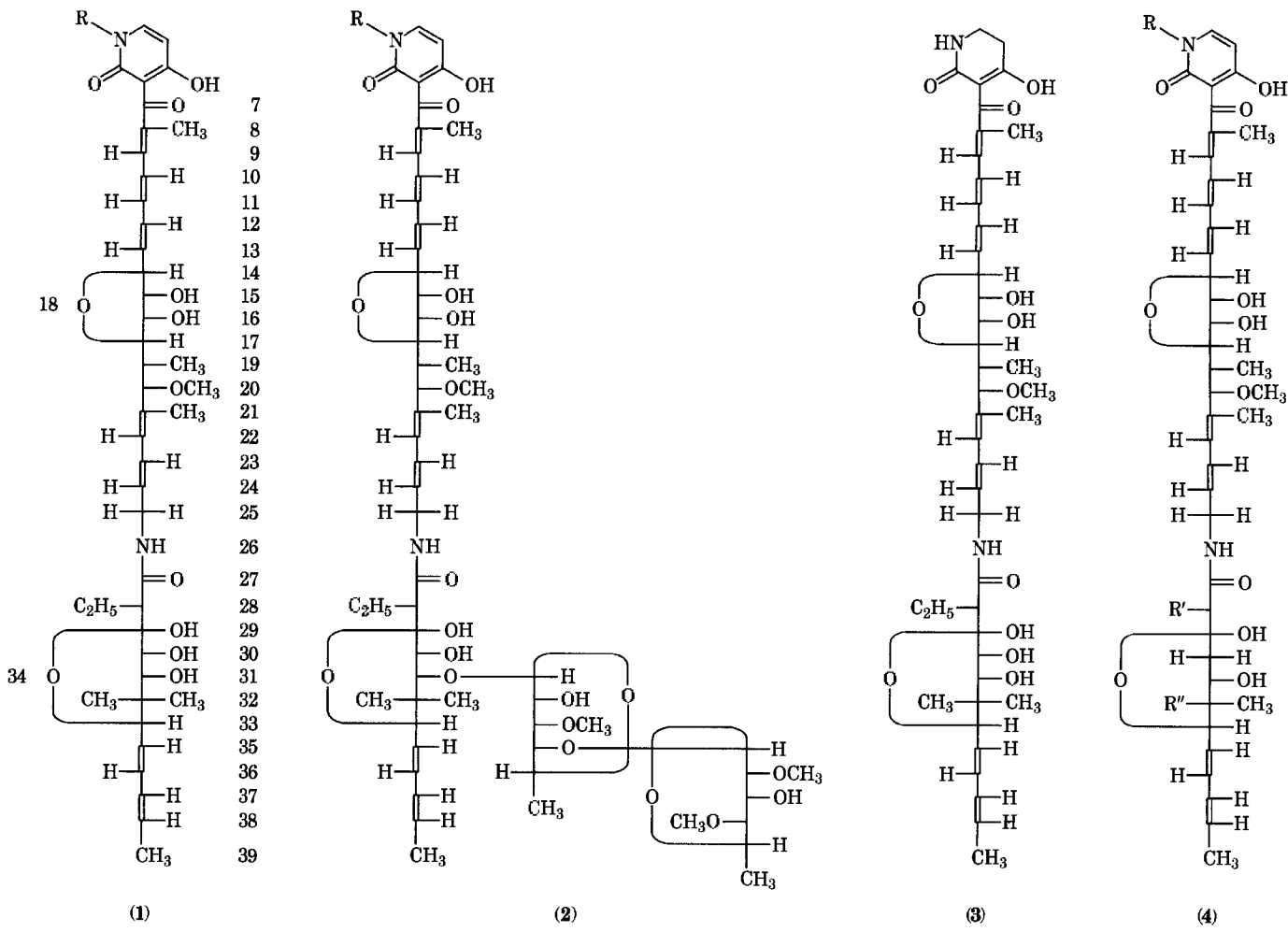


Fig. 1a. Structures of the elfamycins given in Table 1 where the carbon skeleton numbering scheme is shown for structure (1) only.

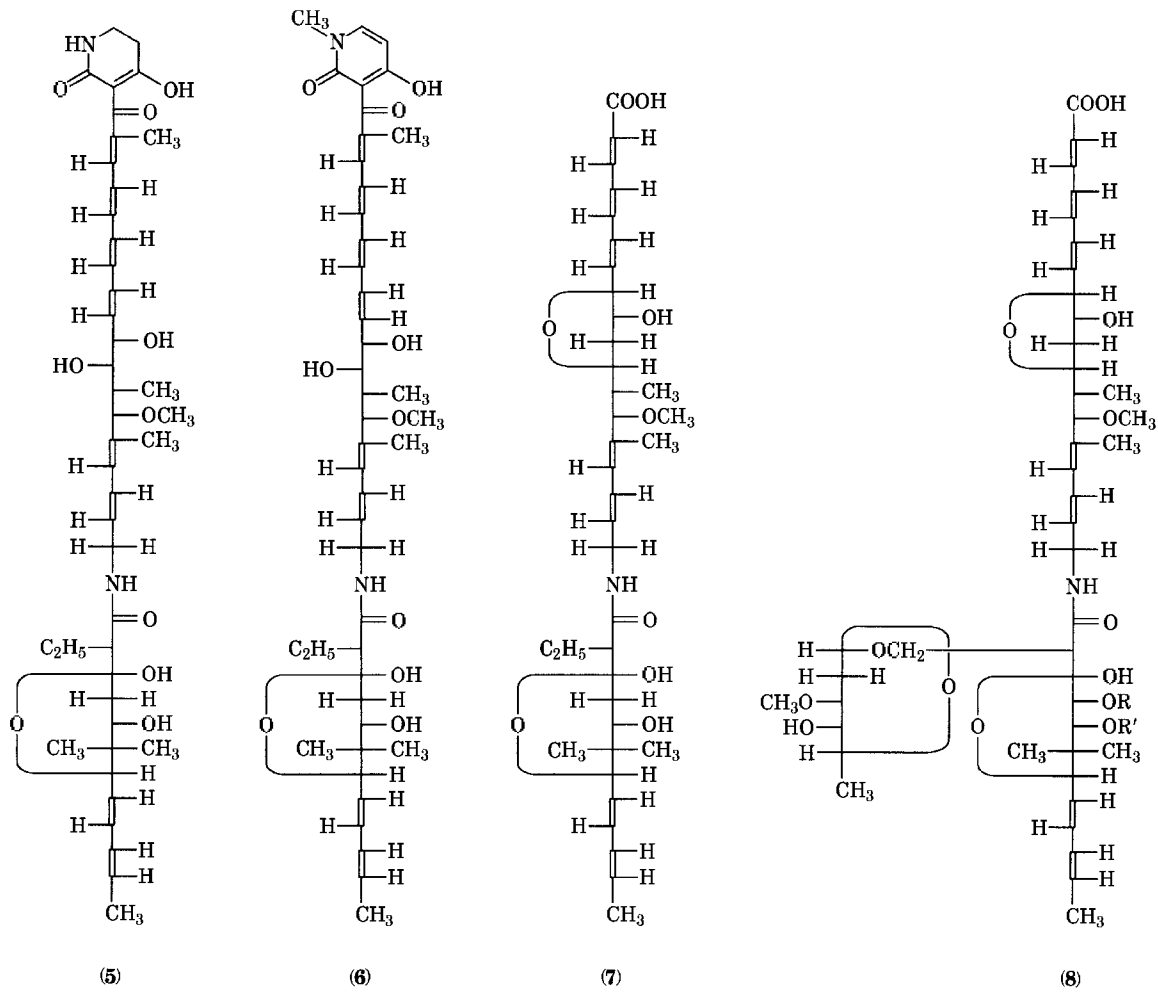


Fig. 1b. Continued

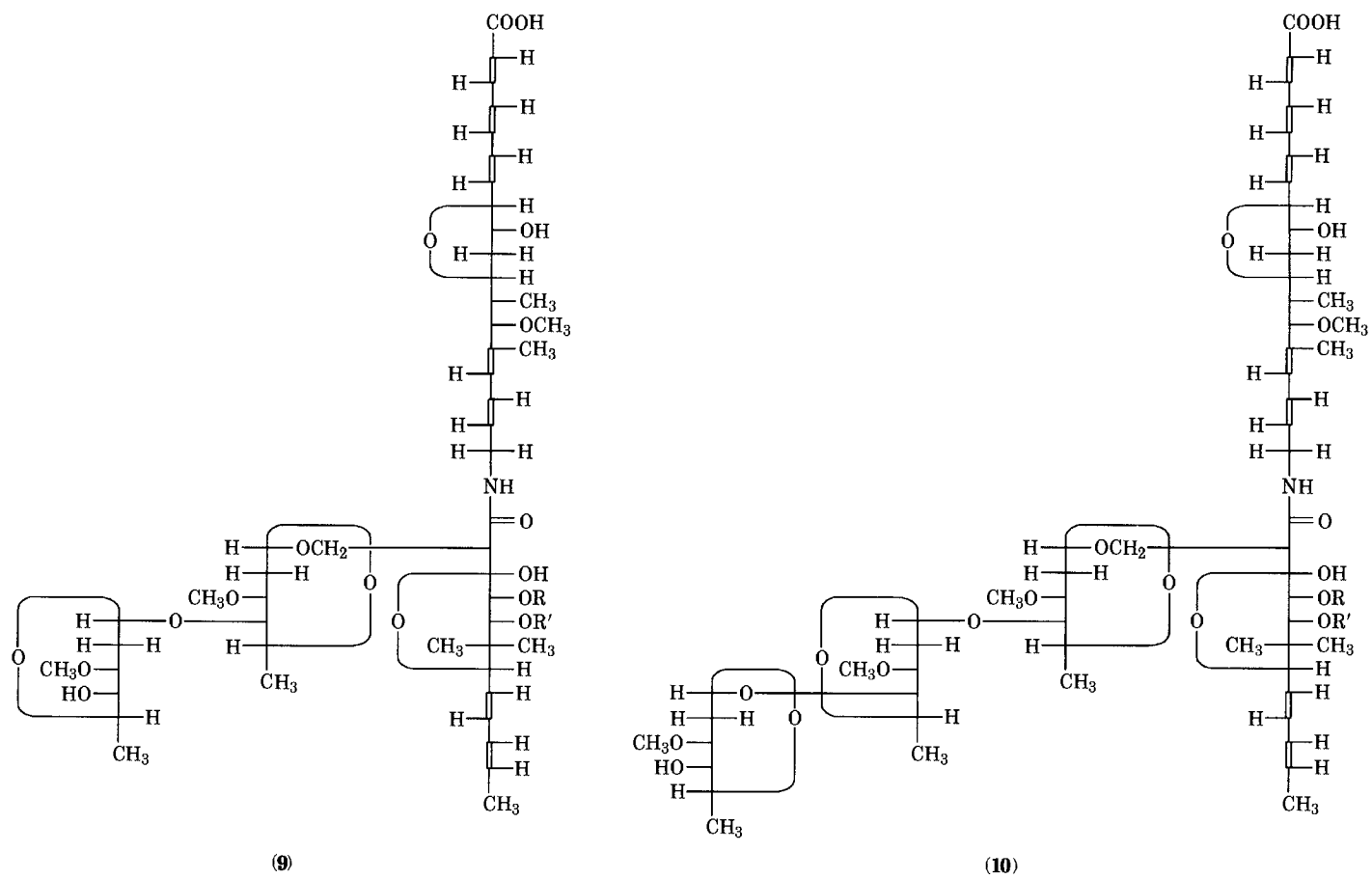


Fig. 1c. Continued

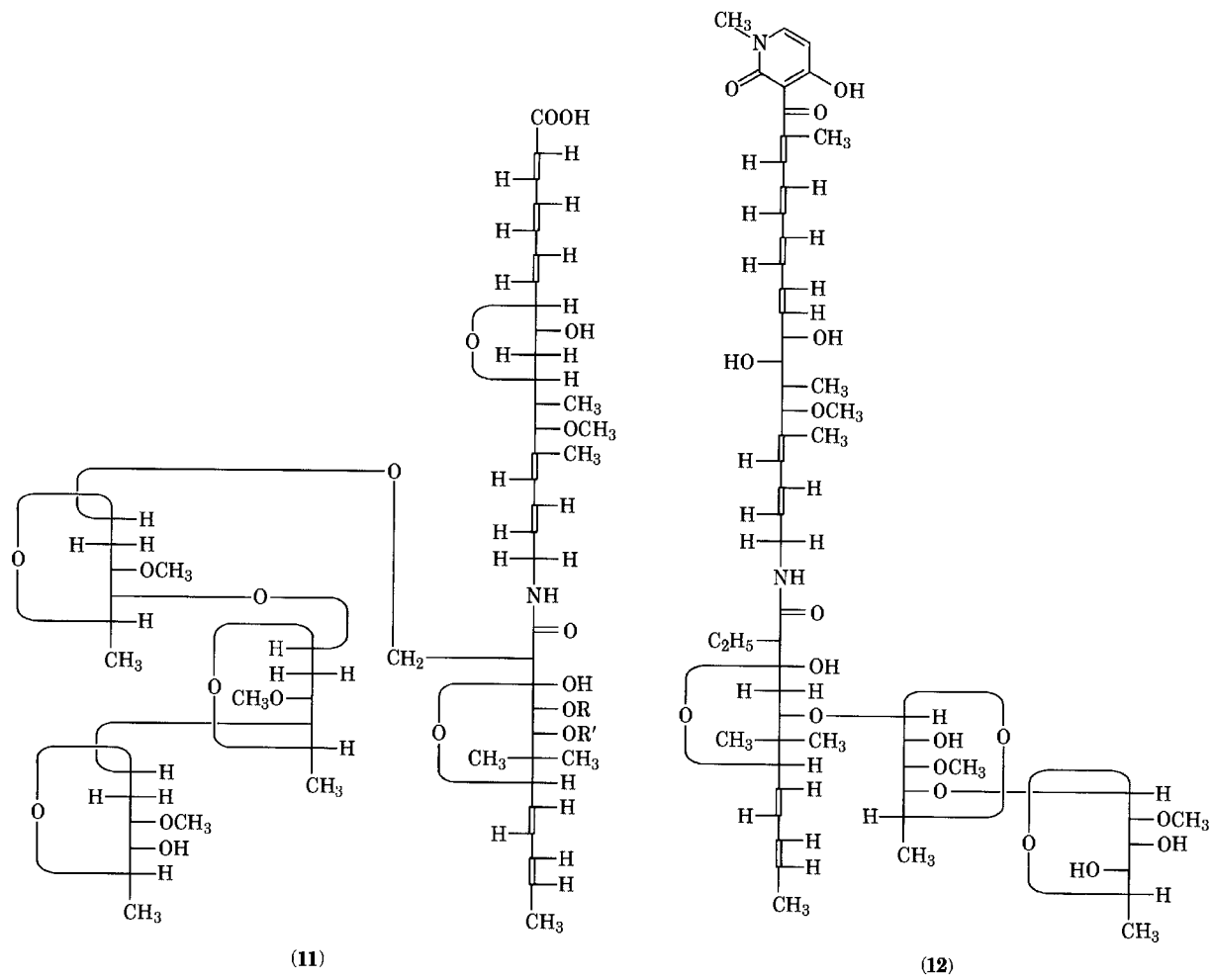


Fig. 1d. Continued

Elfamycins are natural products. Aurodox (1, R = CH₃) and efrotomycin (2, R = CH₃) have been synthesized chemically.

Properties

Elfamycins are slightly acidic because of the 4-hydroxy-2-pyridone or the carboxylic acid moiety. They are soluble in most polar organic solvents and the alkali and ammonium salts are water-soluble. The extractability of the free acids from aqueous solution into solvents such as dichloromethane and ethyl

acetate is utilized in their isolation from fermentation broths.

Purifications of elfamycins have been described in the literature using Craig distribution (2,34), chromatography on Sephadex LH-20 (2,14,26) and Amberlite XAD-2 (10,17,19,26), supercritical fluid extraction (37), and chromatography on an Ito multilayer coil planet centrifuge (26,38). ^1H and ^{13}C nmr assignments of most elfamycins have been accomplished (3,24,26,32). The characteristic uv spectra permits some differentiation (12) and bathochromic shifts associated with Al^{3+} complexation have been used to quantify efrotomycin (**2**, $\text{R} = \text{CH}_3$) in feed premixes (39,40).

Structures. The first structure to be elucidated was that of aurodox (**1**, $\text{R} = \text{CH}_3$), the oldest member of the elfamycin family. The elfamycins are amorphous and crystalline derivatives are as yet unknown. A combination of degradation reactions and the spectroscopic and Roentgen crystallographic analyses of the products was used to determine structure (4). The discovery that the amide linkage in aurodox could be disconnected under extremely mild conditions permitted a sequence of controlled cleavages, the products of which provided the structural and stereochemical information required to permit complete stereochemical assignments of the parent molecule. As shown in Figure 2a, treatment of aurodox using acetic acid at room temperature gave several products. One, termed goldinonic acid in view of the aurodox-producing microorganism's name, represented the carboxylic acid component of the amide and was isolated as the γ -lactone (**13**) (41). Periodate oxidation gave 3(*S*)-4(*E*)-6(*Z*)-3-hydroxy-2,2-dimethyl-4,6-octadienal (**14**), the absolute configuration of which was ascertained crystallographically (40) and by further degradation via (**15**) and (**16**) to the retrosynthetically significant (*R*)-(---)-pantolactone (**17**). Repetition of the acetic acid treatment using aurodox (4-bromobenzyl)ether (**19**) as substrate minimized side reactions and gave goldinonolactone (**13**) and the amine component, goldinamine (4-bromobenzyl)ether (**20**), thus accounting for all skeletal elements of the antibiotic.

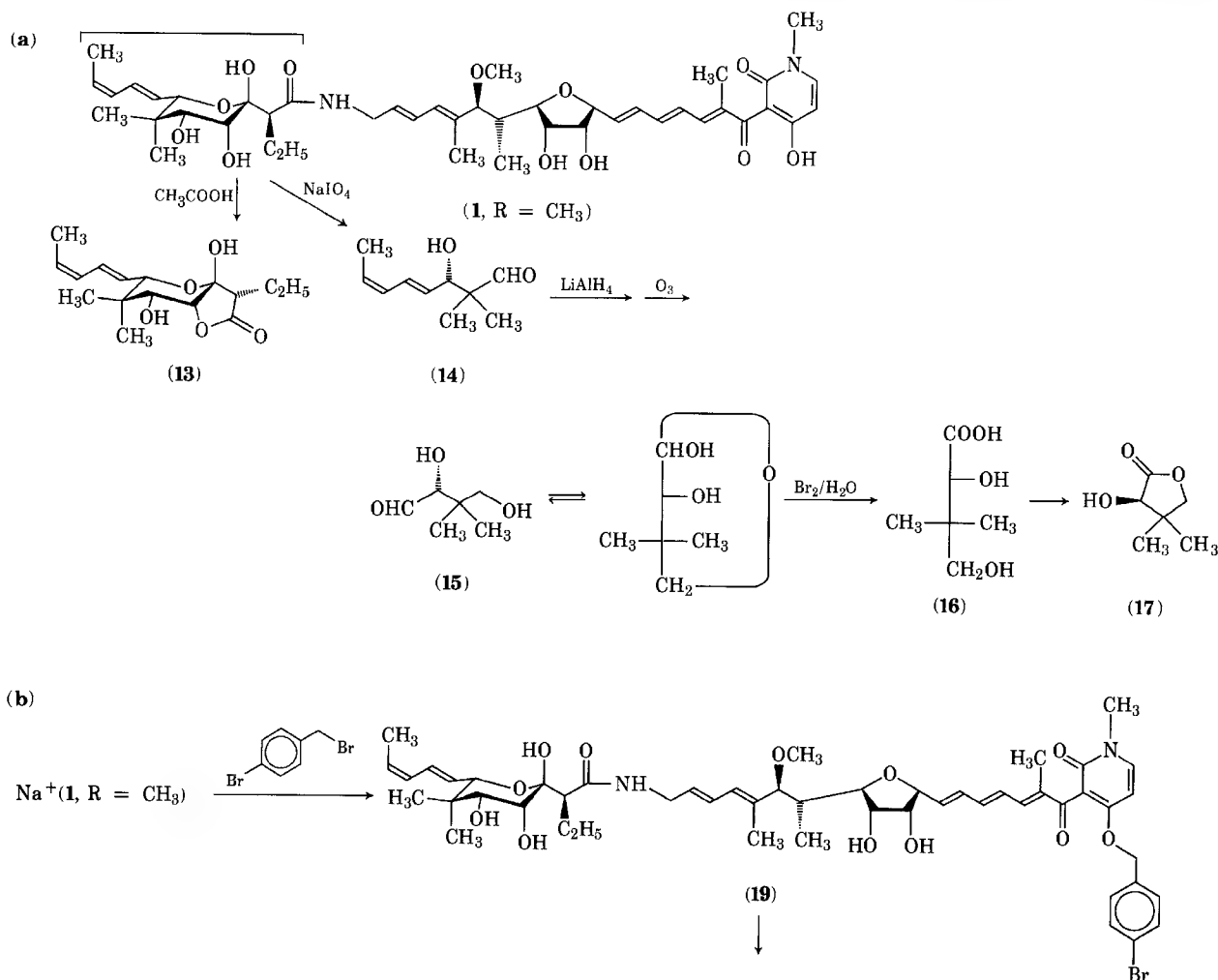


Fig. 2a.

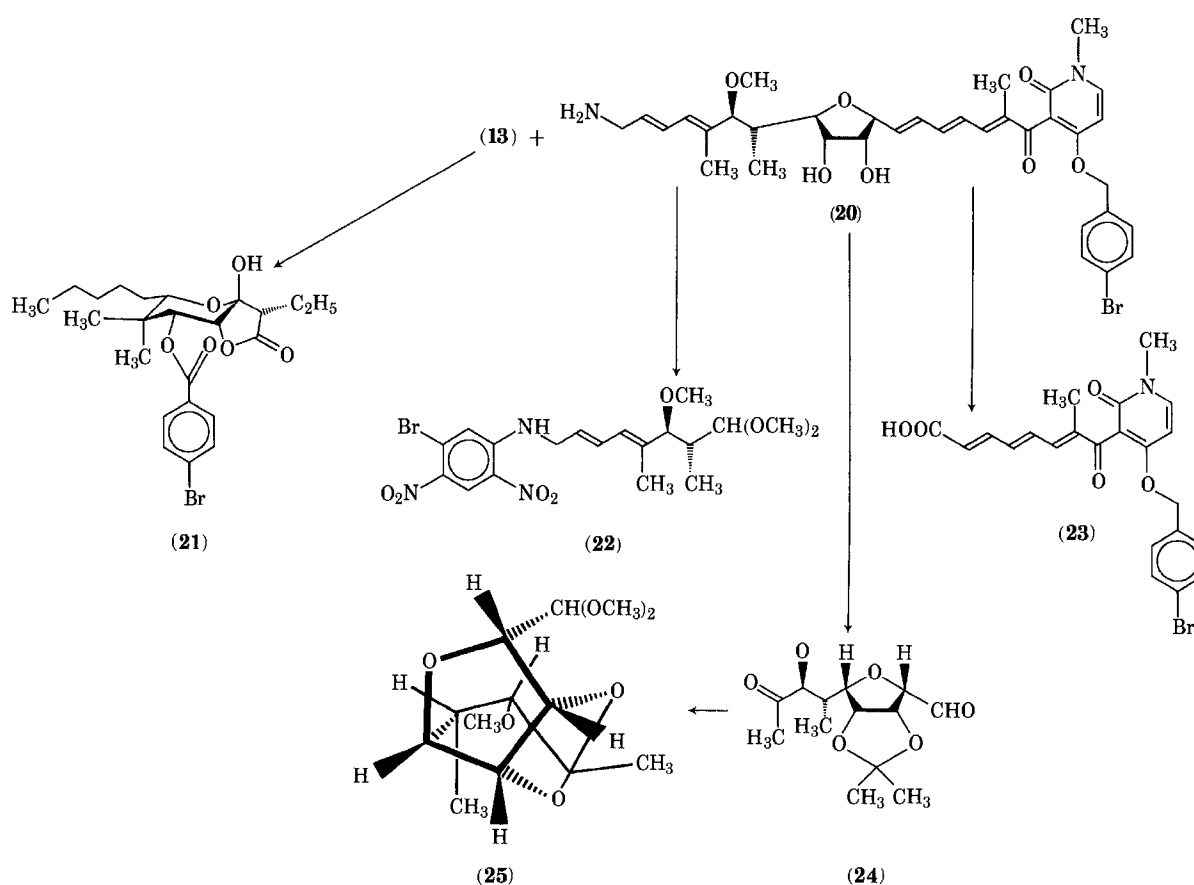


Fig. 2b. Chemical degradation of aurodox: (a), goldinonic acid; (b), goldinamine.

The goldinamine bromobenzyl ether (20) gave rise to a series of useful degradation products. The most significant fragments are summarized in Figure 2b. The spectroscopic analysis of the trienone moiety was supplemented crystallographically via its derivative (23) (42), and the absolute configuration of (13) was confirmed by crystallographic analysis of the 4-bromobenzoate (21) (4,41).

The diene side of (20) was first obtained from its *N*-acetyl derivative by periodate oxidation in the form of 2(*R*)-3(*S*)-4(*E*)-6(*E*)-8-amino-3-methoxy-2,4-dimethyl-4,6-octadienal (4,43). The threeo configuration of this product was ascertained by ir spectroscopy (4) and by crystallographic analysis of the *N*-dinitrophenyl (DNP) derivative of its dimethyl acetal (43). Anomalous scatter in the analysis of (22) made the determination of absolute configuration possible (44). The configuration of the central tetrahydrofuran ring in (20) was originally determined spectroscopically (43,45) and its topography was revealed by several degradation products (4). Most significant was the isolation of (24) which included not only the two stereocenters of (22), but also the four carbons in the tetrahydrofuran ring. Aldehyde (24) was converted to the crystalline tricyclic acetal (25). The topographic assignment of (25) also resulted from a crystallographic analysis (46), so that aurodox (1, *R* = CH₃) became known in complete stereochemical detail.

Similar degradation reactions were used to establish the absolute configuration of mocimycin (kirromycin) (1, *R* = H) (46), the constitution of which had been described previously (7,47). The chemical structures of most other subsequently discovered elfamycins have been determined spectroscopically and assignments of absolute configurations are not complete. The elfamycin structures shown in Figure 1 have complete stereochemical details that have been in part ascertained experimentally and in part are assumed to correspond to the aurodox topography.

Production, Biosynthesis, and Chemistry

The production of elfamycins is described in the references cited in Table 1. Fermentation yield improvements with aurodox (1, *R* = CH₃) proved difficult because of feedback inhibition (48). Aurodox-resistant strains (49), however, responded positively to conventional mutagenic methods leading to yield increases from 0.4 to 2.5 g/L (50). Scale-up of efrotomycin (7, *R* = CH₃) fermentations were found to be particularly sensitive to small changes in sterilization conditions of the oil-containing medium used (51).

Biosynthetic studies using acetate (Ac), propionate (Pr), and butyrate (Bu) revealed the polyketide nature of aurodox which has the composition Pr(Ac)₈ for the goldinamine skeleton C-7 to C-25 and the composition Bu(Ac)₅ for the C-27 to C-39 carbon chain of goldinonic acid. In contrast to the methyl branch at C-8, those at C-19 and C-21 are methionine-derived as are all remaining methyl groups (52,53). The biogenetic origin of the pyridone moiety is not clear.

Desmethylefrotomycin (2, *R* = H) is a product of microbial transformation of mocimycin (1, *R* = H) by *Nocardia* ATCC 53758 (35). Efrotomycin (2, *R* = CH₃) biosynthesis was studied in a resting cell system of *Nocardia lactamdurans* by glycosylation of aurodox (1, *R* = CH₃) via 6'-deoxyallosyl aurodox (54).

Mocimycin has been chemically converted to aurodox by protection of the 4-hydroxy group at the pyridone moiety as the benzoylformate, followed by *N*-methylation and hydrolytic removal of the protective group (1,55). Whereas aurodox esters are active growth promoters in animals, goldinamines that are *N*-acylated by acids other than goldinonic acid, such as acetic, benzoic, or arylsulfonic acids, lack useful antimicrobial or growth-promoting activity (1).

Mocimycin was prepared from dihydromocimycin (3) by oxidation with selenium dioxide (14,56). 4-Amino-4-dehydroefrotomycins were obtained by aminolysis of efrotomycin-4-*O*-phenylchlorophosphate (57).

Elfamycins having 4-hydroxy-2-pyridone moieties (1–6,12) readily undergo reversible internal cyclizations by conjugate addition of either oxygen functionality on the pyridone ring at C-9. These products can be isolated as exemplified by isofrotomycin (58).

Aurodox and efrotomycin have been chemically synthesized (59). In analogy to the degradation studies shown in Figure 2, goldinonolactone (13) was synthesized from (17) by enantioselective reduction of ketolactone (26) followed by a sequence of acyclic stereoselective reactions shown in Figure 3. The stereocenters C-30 and C-31 in goldinonic acid (1) were generated by a Sharpless epoxidation of (29) followed by inversion at C-2 in epoxyalcohol (31). The (*E*),(*Z*)-geometry of the pentadienyl substituent was constructed from (35) by oxidation and addition of the anion derived from (*Z*)-crotyl diphenylphosphine oxide. Addition of butyrate to lactone (36) afforded a mixture of lactols which, after acetal hydrolysis, recyclization, and base-catalyzed epimerization, gave a mixture of C-3-epimeric dihydroxylactols from which pure goldinonolactone (13) could be isolated chromatographically (60).

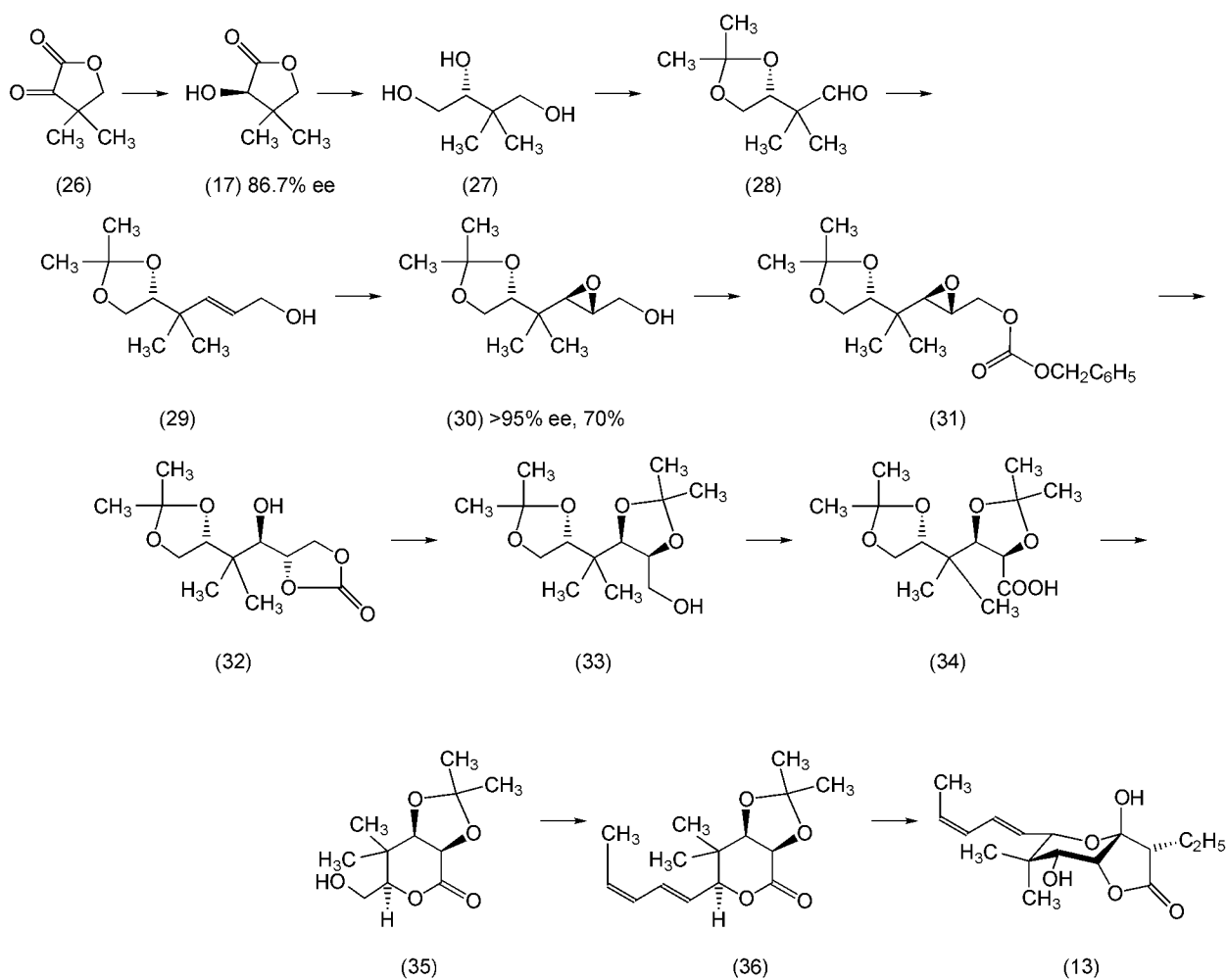


Fig. 3. Synthesis of goldinonolactone (13).

The all-cis tetrahydrofuran ring of goldinamine was synthesized by the consecutive epoxide opening of the ester enolate derived from (42) according to an old concept as shown in Figure 4 (61). The five adjacent stereocenters in (42) were assembled by a kinetic resolution of alcohol (38) via its epoxide (39). One of the newly gained stereocenters was sacrificed to gain the allylic alcohol (40) which was subjected to a Sharpless epoxidation to introduce the third stereocenter. An epoxidation of the homoallylic alcohol (41) using *m*-chloroperbenzoic acid generated the two additional stereocenters with a diastereoselectivity of 94%. Hydrogenolysis of the benzyl ether, hydrolysis of the silyl ether, protection of the resulting diol, and oxidation of the primary alcohol gave a carboxylic acid which, after deprotonation, generated an alkoxide ion that opened the terminal epoxide to furnish the desired tetrahydrofuran (43). Further elaboration via (44) and (45) gave the terminal alkene (46) which was subjected to a stereoselective hydroboration to introduce the fifth consecutive stereocenter. A Swern oxidation of the resulting alcohol, followed by reaction with lithium di(α -methoxyvinyl)cuprate, led to the vinyl ether (48), the hydrolysis of which gave (49) with the sixth stereocenter in 73% de. A Wittig-Horner reaction using trimethyl phosphonoacetate established the (*E*)-geometry of the alkene with a stereoselectivity of 78%. An additional reduction step led to aldehyde (50).

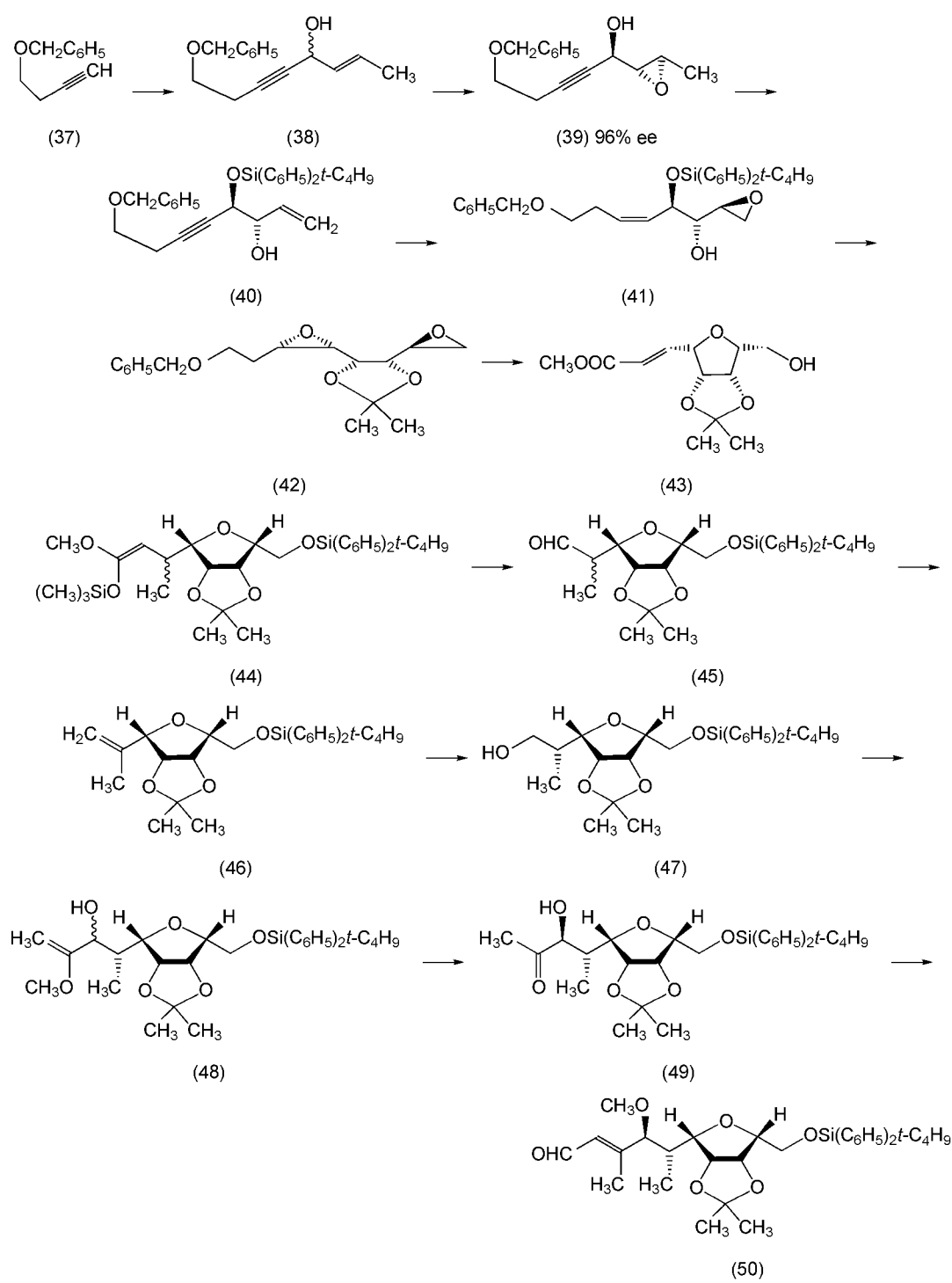


Fig. 4. Synthesis of the tetrahydrofuran moiety in goldinamine.

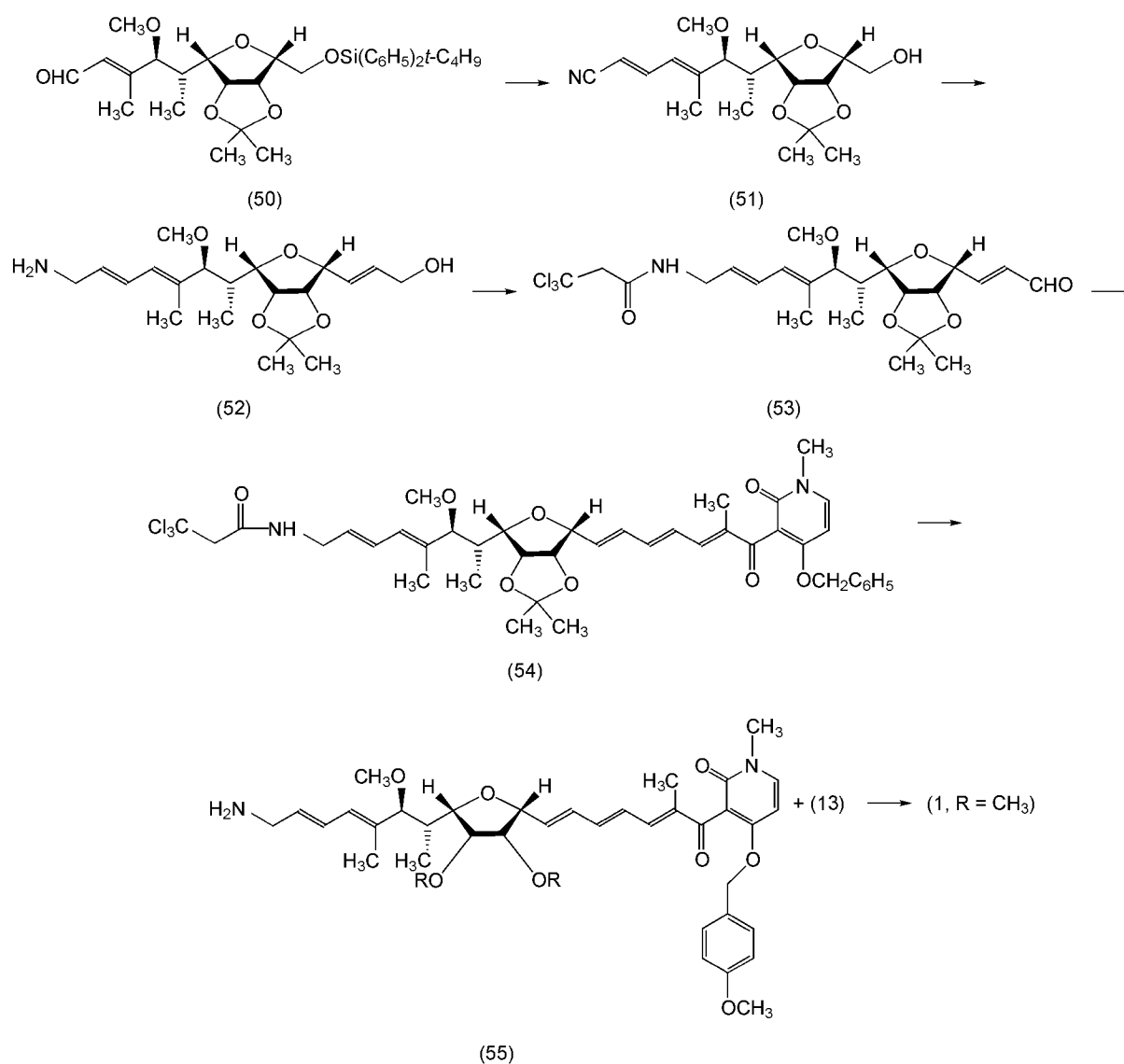


Fig. 5. Synthesis of goldinamine derivatives and aurodox when R' is trimethylsilane.

Condensation of (50) with diisopropyl phosphonoacetone nitrile established the second (*E*)-alkene with 82% stereoselectivity as shown in Figure 5. The third (*E*)-alkene, as shown in (52), was prepared from (51) after desilylation and oxidation of the resulting primary alcohol, followed by an additional Wittig-Horner reaction with 75% stereoselectivity. The missing (*E*),(*E*)-diene portion was generated by a Wittig-Horner condensation where one of the double bonds was provided by the reactant (*E*)-3-methyl-4-[4-(benzyloxy)-1,2-dihydro-1-methyl-2-oxo-3-pyridyl]-4-oxo-2-butenyl-1-triphenyl phosphonium bromide. Goldinamine derivative (55), derived from (54) by changing the protective groups, served as a suitable substrate for the final condensation with (13) to furnish aurodox (1, R = CH₃), after removal of the silyl and benzyl ether groups (62).

Goldinonolactone and the tetrahydrofuran moiety of goldinamine were also synthesized from L- and D-mannose, respectively (63). The synthesis of efrotomycin has also been effected (62).

Biological Properties

Mode of Action. Elfamycins block bacterial protein biosynthesis at the level of elongation factor Tu (EF-Tu) (64–66). The biosynthesis of protein proceeds in four major stages, commencing with activation, which involves the synthesis of aminoacyl-tRNA (aa-tRNA) in the cytoplasm, followed by initiation, elongation, and termination. Binding of the ternary complex EF-Tu-GTPaa-tRNA, where GTP is guanosine triphosphate, in the ribosomal A-site initiates the elongation phase. After hydrolysis of GTP to guanosine diphosphate (GDP) and the subsequent release of EF-Tu, peptide bond formation takes place. Elfamycins prevent the release of the EF-Tu-GDP complex from the ribosome and hence debilitate peptidyl transfer and peptide synthesis. This mode of action stands in unique contrast to that of other antibiotics which also interfere with the elongation phase of protein biosynthesis (60).

Antimicrobial Activity. The elfamycins' antimicrobial specificity and lack of toxicity in animals can be explained in view of species-dependent specificity of elfamycin binding to EF-Tu. Inefficient cellular uptake or the presence of a nonresponding EF-Tu were cited as responsible factors for the natural resistance in *Halobacterium cutirubrum* (67), *Lactobacillus brevis* (68), and in actinomycetes (5,69). The low activity of elfamycins against *S. aureus* was also attributed to an elfamycin-resistant EF-Tu system (70). However, cross-resistance with other antibacterial agents has not been observed (71).

Elfamycins have similar *in vitro* antimicrobial spectra and the activity against *Moraxella*, *Pasteurella*, *Yersinia*, *Haemophilus*, *Streptococcus*, *Corynebacterium*, and *Neisseria* appears to be common (2,23,72). Aurodox (1, R = CH₃) (2), azdimycin (8), LL-E19020α (11, R = H, R' = COCH₂C₂H₅), LL-E19020β (11, R = COCH₂C₂H₅, R' = H) (29), efrotomycin (2, R = CH₃), and heneicomycin (4, R = R'' = CH₃, R' = C₂H₅) (72) have shown activity *in vivo* against *Streptococcus pyogenes* and the latter two antibiotics exhibited similar activity against *Moraxella bovis* (73,74).

Kirrothricin (5), aurodox, and efrotomycin were found to be active as protozoacids against the parasite *Eucoccidium dinophilii* (75), and LL-E19020α and LL-E19020β were active against *Babesia* (see ANTIPARASITIC AGENTS). The latter two antibiotics acted as nematocides toward *Caenorhabditis elegans* and as anthelmintics (see ANTIPARASITIC AGENTS, ANTHELMINTICS) toward *Trichostrongylus colubiformis* (28).

Mocimycin (kirromycin) (1, R = CH₃) and tylosin [1401-69-0] (see ANTIBIOTICS, MACROLIDES) exhibited similar activity against *Treponema hyodysenteriae*, the causative microorganism of dysentery in swine. Dihydromocimycin (3), however, was more active against this microorganism than either mocimycin or tylosin (14). Moreover, dihydromocimycin was active against tylosin-resistant *Treponema* strains and was used as a feed additive at levels of 20–40 ppm (see FEEDS AND FEED ADDITIVES) (14). The growth-promoting activity of mocimycin was not observed for dihydromocimycin (14).

Efrotomycin (2, R = CH₃) is active against mycoplasma (PPLO) of chicks, pigs, and cattle (9). A combination of efrotomycin and bottromycin [1393-68-6], a complex of macrolides, has been used as a therapeutic and prophylactic agent to control mycoplasma infections and dysentery in swine (76). *Mycoplasma gallisepticum* S-6 was the most susceptible organism tested against heneicomycin (4, R = R'' = CH₃, R' = C₂H₅) (15,16). Additionally, *M.*

gallisepticum infected chicks receiving feed containing 50 ppm of LL-E19020 α (**11**, R = H, R' = COCH₂C H₃) had better weight gain, improved feed conversion, and less mortality than infected, nonmedicated chicks (30).

Efrotomycin is effective against *Clostridium perfringens* (77) and is much more active against 29 clinical isolates of *Clostridium difficile* than ciprofloxacin [85721-33-1] (78,79) (see ANTIBACTERIAL AGENTS, SYNTHETIC, QUINOLONES). Activity against gram-positive anaerobes, especially *Clostridium difficile*, was also noted for all phenelfamycins and unphenelfamycin (**8**, R = R' = H). Phenelfamycin A (**8**, R = H, R' = COCH₂C H₃) prolonged the survival of *C. difficile* enterocolitis in infected hamsters and was active against *Neisseria gonorrhoeae* and *streptococci* (80). Aurodox (**1**, R = CH₃) exhibited similar activity in the hamster model (81).

Antibiotic LL-E19020 α and LL-E19020 β are described as useful agents for the treatment of chronic respiratory disease, fowl cholera, and necrotic enteritis in birds (76) and as anthelmintics in monogastric and ruminant animals (28).

Growth Promotion. Elfamycins, in general, enhance the growth of farm animals (see GROWTH REGULATORS, ANIMAL). Growth improvement and feed conversion was studied using aurodox (**1**, R = CH₃) in chicks and turkeys. Effective drug levels were established to be 1–10 mg/kg of feed for chicks. The effective dose for turkeys was 5–10 times higher (82). The growth promoting ability of aurodox (**1**, R = CH₃) and mocimycin (**1**, R = H) was compared with other antibiotics and hormonal anabolic agents in chicks (83). Maximum weight improvement of 23% and enhanced feed efficiency of 13% in chicks was obtained with efrotomycin (**2**, R = CH₃) levels of 11 ppm (77). Antibiotics LL-E19020 α and LL-E19020 β proved to be more effective growth promoters in chicks than bacitracin [1405-87-4] and virginiamycin (see ANTIBIOTICS, PEPTIDES) (32) and also improved feed efficiency for meat-producing animals and fish. When given at 100 ppm in feed they caused weight gain by 6.1% in chicks. Feed efficiency was also increased, and during the first week of feeding an 8% increase was observed (84). Antibiotics LL-E19020 α and LL-E19020 β are more effective growth promoters than aurodox (32). The growth promoting effect of zinc bacitracin was potentiated by mocimycin (85). The improvement of weight gain and feed conversion by subtherapeutic antibiotic levels were shown to occur concomitantly with decreased cholytaurine hydrolase activity suggesting that the inhibition of this enzyme is responsible for weight gain and improvement in feed utilization (see ENZYME INHIBITION) (86).

Efrotomycin (**2**, R = CH₃) is being developed as a growth promoting agent for swine. Pigs on efrotomycin diets gained weight 5.9–8.9% faster and utilized feed 1.7–4.0% more efficiently than the control animals. Growth improvement was linear from 2 to 16 ppm of drug, and the plateau of feed efficiency was reached at 4 ppm of efrotomycin (87). The effect on the shedding of *Salmonella*, however, is a matter of primary concern in swine and fowl, not only with efrotomycin (88), but with other elfamycins as well.

Stable growth promoting feed additives were prepared by granulation of the drug with alginic acid [9005-32-7] and magnesium hydroxide and adding it to oiled rice hulls (89) or by adsorption of elfamycins onto corn cob grits and coating with 10% tristearin [555-43-1] (90). A molecular efrotomycin dispersion with (2-vinylpyridine)-styrene copolymer served as a postrumen effective dosage form for oral administration (91).

Improvement of Lactation. Qualitative and quantitative improvements in milk production (see MILK AND MILK PRODUCTS) are dependent upon changes of ruminal volatile fatty acid (VFA) production and VFA composition. Increased propionate production at the expense of acetate and butyrate is responsible for growth enhancement and is achieved by additives such as polyether antibiotics (see ANTIBIOTICS, POLYETHERS). Relatively high levels of acetate and butyrate, however, are required to maintain adequate fat content in milk. Oral administration of elfamycins at concentrations of 1–10 mg/kg of animal body weight per day has been shown to increase milk volume from 2–15% relative to untreated animals without compromising fat content. The methods of administration to ruminants such as dairy cows and goats were similar to those employed for improving feed utilization and growth promotion (92).

Economic Aspects

The potential usefulness of elfamycins as growth promoters and feed-conversion enhancers is now generally recognized. Low original fermentation yields and difficulties in yield improvements discouraged early attempts to develop aurodox (**1**, R = CH₃) and mocimycin (kirromycin) (**1**, R = H) commercially. A development program for efrotomycin (**2**, R = CH₃), however, is ongoing as of this writing. Some of the newer elfamycins, such as the LL-E19020 pair, are considerably more active growth promoters than either aurodox or mocimycin, pointing toward the emergence of a second generation of elfamycins.

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GLYCOPEPTIDES (DALBAHEPTIDES)

The vancomycin–ristocetin family of glycopeptides (1,2) is a subclass of linear sugar-containing peptides composed of seven amino acids cross-linked to generate a specific stereochemical configuration. This configuration forms the basis of a particular mechanism of action, eg, complexation with the D-alanyl-D-alanine terminus of bacterial cell wall components (3,4). Because the mechanism of action is the distinguishing feature of these peptides, the term dalbaheptide, from D-al(anyl-D-alanine)b(inding)a(ntibiotics) having hept(aept)ide structure, has been proposed to distinguish them within the larger and diverse groups of glycopeptide antibiotics (5).

About 40 different naturally produced dalbaheptides have been reported (Table 1), which correspond to a larger number of chemical entities (Tables 2–6). Many of these antibiotics are groups of strictly related factors called complexes. Among them, vancomycin (39) (Table 4) (6) and the teicoplanins (18–22) (Table 3) (7) are used clinically as a result of high activity against gram-positive pathogens such as many coagulase-negative *Staphylococci* (CNS), *corynebacteria*, *Clostridium difficile*, multiresistant *Staphylococcus aureus*, and highly gentamicin-resistant *Enterococci* which are refractory to established drugs. Eremomycin (52) (Table 4) is under clinical evaluation (8). Many patents claim feed-utilization efficiency increase and growth promotion in domestic animals for several dalbaheptides but only avoparcin (63) (Avotan) (Table 5) is commercially used. The platelet aggregation ability of ristocetin A (1) (Table 2) renders it a suitable diagnostic agent for von Willebrand's disease, a hematologic disorder of genetic origin (9).

Table 1. Naturally Occurring Dalbaheptides

Antibiotic	Producing organism	Year ^a	Company or Institute	Refs.
ristocetin A, B	<i>Nocardia lurida</i> NRRL 2430	1953	Abbott	1,2
vancomycin	<i>Streptomyces orientalis</i> NRRL 2450	1955	Lilly	1,6,10–13
actinoidin A, B	<i>Proactinomyces actinoides</i>	1956	Research Institute for the Discovery of New Antibiotics, Moscow	1,18,19
K-288	<i>Streptomyces haranomachiensis</i> n.sp	1961	Tohoku University, Sendai	20
ristomycin A, B	<i>Proactinomyces fructiferi</i> var. <i>ristomycini</i>	1962	Research Institute for the Discovery of New Antibiotics, Moscow	1,2
avoparcin (LL-AV290 complex)	<i>Streptomyces candidus</i> NRRL 3218	1966	American Cyanamid	21–24
AM374	<i>Streptomyces eburosporeus</i> NRRL 3582	1969	American Cyanamid	25
A477	<i>Actinoplanes</i> sp. NRRL 3884	1971	Lilly	26
actaplanin (A4696 complex)	<i>Actinoplanes missouriensis</i> ATCC 23342	1971	Lilly	27–29
AB-65	<i>Saccharomonospora viride</i> T-80	1973	Dainippon Pharmaceuticals	30
teicoplanin (teichomycin complex)	<i>Actinoplanes teichomyceticus</i> ATCC 31121	1975	Lepetit	7,31–33
A35512 complex	<i>Streptomyces candidus</i> NRRL 8156	1976	Lilly	34–36
OA-7653A, B	<i>Streptomyces hygrosopicus</i> subsp. <i>himasaensis</i> ATCC 31613	1978	Otsuka Pharmaceutical	37,38
A51568A (N-demethyl-vancomycin), B	<i>Nocardia orientalis</i> NRRL 15232	1982	Lilly	39,40
A41030 complex	<i>Streptomyces virginiae</i> NRRL 15156	1982	Lilly	41–43
A47934	<i>Streptomyces toyocaensis</i> NRRL 15009	1982	Lilly	43–45
ardacin (AAD-216 complex, aridicin)	<i>Kibdelosporangium aridum</i> ATCC 39323	1983	Smith, Kline and French	15,46–48
chloropolysporin A, B, C	<i>Faenia interjecta</i> sp. nov. FERM BP-538	1983	Sankyo	49–51
A40926 complex	<i>Actinomadura</i> sp. ATCC 39727	1984	Lepetit	52–54
M43 complex	<i>Nocardia orientalis</i> NRRL 2450	1984	Lilly	55
kibdelin (AAD-609 complex)	<i>Kibdelosporangium aridum</i> subsp. <i>largum</i> ATCC 39922	1985	Smith, Kline and French	56,57
izupeptin A, B	<i>Nocardia</i> sp. FERM P-8656	1986	Kitasato Institute, Tokyo	58
parvodicin (AAJ-271)	<i>Actinomadura parvosata</i> ATCC 53463	1986	Smith, Kline and French	59
synmonicin A, B, C (CWI-785)	<i>Synnemomyces mamnoorii</i> ATCC 53296	1986	Eskayef Ltd.; Smith, Kline and French	60
actinoidin A ₂	<i>Nocardia</i> sp. SKF-AAJ-193	1987	Smith, Kline and French	61,62
orienticin (PA)	<i>Nocardia orientalis</i> PA-42867	1987	Shionogi	63,64
eremomycin	<i>Actinomyces</i> sp. INA-238	1987	Institute of New Antibiotics, Academy of Medical Sciences, Moscow	8,65
A42867	<i>Nocardia</i> sp. nov. ATCC 53492	1987	Lepetit	66
A82846 A, B, C	<i>Amycolatopsis orientalis</i> NRRL 18098	1987	Lilly	67–70
UK-68,597	<i>Actinoplanes</i> sp. ATCC 53533	1987	Pfizer	71,72
helvecardin A, B	<i>Pseudonocardia compacta</i> subsp. <i>helvetica</i> SANK 65185	1988	Sankyo	73
chloroorienticins A, B, C, D, E (PA-45052)	<i>Amycolatopsis orientalis</i> PA-45052	1988	Shionogi	69,74,75
A80407 A, B	<i>Kibdelosporangium philippinensis</i> NRRL 18198	1989	Lilly	76
MM 45289, MM 47756	<i>Amycolatopsis orientalis</i> NCIB 12531	1989	Beecham	77
MM 47761, MM 49721	<i>Amycolatopsis orientalis</i> NCIB 12608	1989	Beecham	78

MM 47766, MM 47767, MM 55256, MM 55260	<i>Amycolatopsis orientalis</i> NCIB 40011	1989	Beecham	79
MM 49728, MM 55266, MM 55267, MM 55268	<i>Amycolatopsis</i> sp. NCIB 40089	1989	Beecham	80
decaplanin	<i>Actinomyces</i> sp. DSM 4763	1990	Hoechst	81
UK-72,051	<i>Amycolatopsis orientalis</i> n.sp.	1990	Pfizer	82

^a Year of patent or first publication.

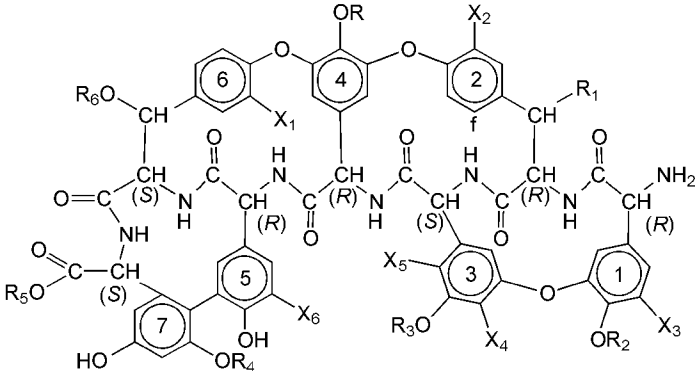


Table 2. Naturally Occurring Ristocetin-type Dalbaheptides

Antibiotic	CASRegistr yNumber	Structure ^a													
		N o.	R	R ₁	R ₂	R ₃	R ₄	R ₅	R	X 1	X 2	X 3	X ₄	X 5	X
ristocetin															
A ^b	[11021-66-2 /	(1)	L-rha → D-glu → D-man → D-ara	O	H	H	D-ma n	C	L-ria	H	H	H	C	H	H
B ^c	[1405-59-01 /	(2)	L-rha → D-glu	O	H	H	D-ma n	C	L-ria	H	H	H	C	H	H
actaplanin															
A	[88357-81-7 /	(3)	D-glu ← man	H	H	D-ma n	D-ma n	C	L-ria	C	H	H	C	H	H
B ₁	[88357-82-8 /	(4)	D-glu ← rha	H	H	D-ma n	D-ma n	C	L-ria	C	H	H	C	H	H
B ₂	[88357-83-9 /	(5)	D-glu	H	H	D-ma n	D-ma n	C	L-ria	C	H	H	C	H	H
B ₃	[88357-84-0 /	(6)	D-glu ← man	H	H	H	D-ma n	C	L-ria	C	H	H	C	H	H
C ₁	[88357-85-1 /	(7)	D-glu ← L-rha	H	H	H	D-ma n	C	L-ria	C	H	H	C	H	H
C ₃	[88357-88-4 /	(8)	D-glu	H	H	D-ma n	H	C	L-ria	C	H	H	C	H	H
G	[88381-73-1 /	(9)	D-glu	H	H	H	man	C	L-ria	C	H	H	C	H	H
A35523 B	[63849-30-9 /	(10)	glu ← rha	O	H	fuc	man	C	3-epi-L-van	H	H	H	H	C	H
A41030															
A	[89139-41-3 /	(1)	H	H	H	H	H	H	H	C	C	H	H	H	C
B	[89139-42-4 /	(12)	H	H	H	H	H	H	H	C	C	H	H	H	H
C	[89140-21-6 /	(13)	H	gal	H	H	H	H	H	C	C	H	H	H	C
E	[89139-43-5 /	(14)	H	H	H	H	H	H	H	C	H	H	H	H	H
F	[89140-20-5 /	(15)	H	gal → gal	H	H	H	H	H	C	C	H	H	H	C
A47934	[90039-80-8 /	(16)	H	SO ₃ H	H	H	H	H	H	C	C	H	H	H	C
UK-68,59	[121377-12-6]	(17)	glu ← van	H	H	SO ₃ H	H	H	H	C	C	C	H	H	C

^a Abbreviations are ria = ristosamine, van = vancosamine, man = mannose, rha = rhamnose, glu = glucose, gal = galactose, ara = arabinose, and fuc = fucose.

^b Identical to ristomycin A.

^c Identical to ristomycin B.

^d A C=O group is present instead of the terminal CH—NH₂.

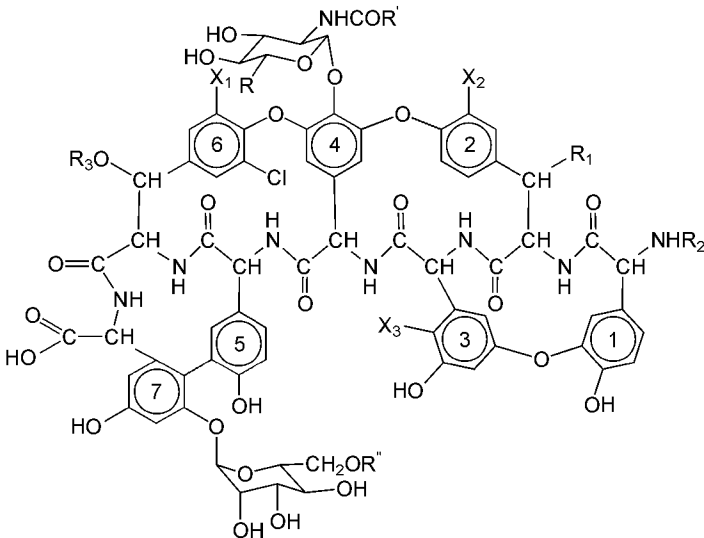


Table 3. Naturally Occurring Ristocetin-type Lipodalbaheptides

Antibiotic	CASRegistryN umber	Structure ^a									
		No .	R	R'	R''	R ₁	R ₂	R ₃	X 1	X 2	X 3
teicoplanin											
T-A2-1	[91032-34-7]	(18)	CH ₂ O	(CH ₂) ₂ CH=CH(CH ₂) ₄ CH ₃	H	H	H	Ac-N-D-glu	H	C 1	H
T-A2-2	[91032-26-7]	(19)	CH ₂ O	(CH ₂) CH(CH ₃) ₂	H	H	H	Ac-N-D-glu	H	C 1	H
T-A2-3	[91032-36-9]	(20)	CH ₂ O	(CH ₂) ₈ CH ₃	H	H	H	Ac-N-D-glu	H	C 1	H
T-A2-4	[91032-37-0]	(21)	CH ₂ O	(CH ₂) CH(CH ₃)CH ₂ CH ₃	H	H	H	Ac-N-D-glu	H	C 1	H
T-A2-5	[91032-38-1]	(22)	CH ₂ O	(CH ₂) ₇ CH(CH ₃) ₂	H	H	H	Ac-N-D-glu	H	C 1	H
ardacin											
A	[95935-21-0]	(23)	COOH	(CH ₂) ₈ CH ₃	H	O	CH 3	H	C 1	C 1	C 1
B	[95935-22-1]	(24)	COOH	(CH ₂) ₇ CH(CH ₃) ₂	H	O	CH 3	H	C 1	C 1	C 1
C	[95935-23-2]	(25)	COOH	(CH ₂) ₈ CH(CH ₃) ₂	H	O	CH 3	H	C 1	C 1	C 1
A40926											
A ^b	[102961-73-9]	(26)	COOH	(CH ₂) ₉ CH ₃	H	H	CH 3	H	H	H	C 1
B ^c	[102961-74-0]	(27)	COOH	(CH ₂) ₈ CH(CH ₃) ₂	H	H	CH 3	H	H	H	C 1
PA	[102961-76-2]	(28)	COOH	(CH ₂) ₉ CH ₃	COCH 3	H	CH 3	H	H	H	C 1
PB ^d	[102961-77-3]	(29)	COOH	(CH ₂) ₈ CH(CH ₃) ₂	COCH 3	H	CH 3	H	H	H	C 1
kibdelin											
A	[103528-50-3]	(30)	CH ₂ O	(CH ₂) ₈ CH ₃	H	O	CH 3	H	C 1	C 1	C 1
B	[103528-49-0]	(31)	CH ₂ O	(CH ₂) ₇ CH(CH ₃) ₂	H	O	CH 3	H	C 1	C 1	C 1
C ₁	[103549-47-9]	(32)	CH ₂ O	(CH ₂) ₈ CH(CH ₃) ₂	H	O	CH 3	H	C 1	C 1	C 1
C ₂	[105997-85-1]	(33)	CH ₂ O	(CH ₂) ₁₀ CH ₃	H	O	CH 3	H	C 1	C 1	C 1
D	[105997-86-2]	(34)	CH ₂ O	(CH ₂) ₂ CH=CH(CH ₂) ₄ CH ₃	H	O	CH 3	H	C 1	C 1	C 1
parvodicin											
A	[114797-09-9]	(35)	COOH	(CH ₂) ₈ CH ₃	H	H	CH 3	H	H	H	C 1
B ₁	[110882-82-1]	(36)	COOH	(CH ₂) ₇ CH(CH ₃) ₂	H	H	CH 3	H	H	H	C 1
C ₂	[110882-85-4]	(37)	COOH	(CH ₂) ₁₀ CH ₃	H	H	CH 3	H	H	H	C 1
C ₄	[110882-87-6]	(38)	COOH	(CH ₂) ₁₀ CH ₃	COCH 3	H	CH 3	H	H	H	C 1

^a Ac-N-D-glu N-acetyl-D-glucosamine.

^b Identical to parvodicin B₂.

^c Identical to parvodicin C₁.

^d Identical to parvodicin C₃.

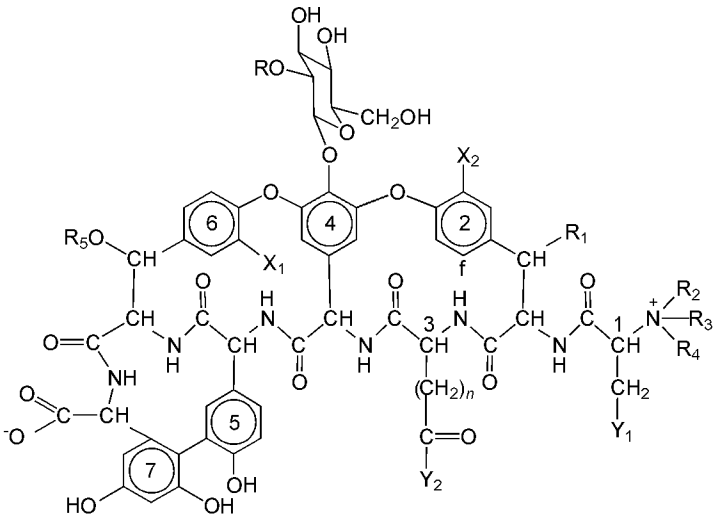


Table 4. Naturally Occurring Vancomycin-type Dalbaheptides

Antibiotic	CASRegistryNumber	Structure ^a											
		No.	<i>n</i>	R	R ₁	R ₂	R ₃	R ₄	R ₅	X ₁	X ₂	Y ₁	Y ₂
vancomycin ^b	[1404-90-6]	(39)	1	L-van	O	H	H	CH ₃	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
OA-7653		)			H					I	I		
A	[73699-70-4]	(40)	2	^c	H	H	CH ₃	CH ₃	D-glu	C	C	H	NH ₂
B	[112219-76-8]	(41)	2	^c	H	H	CH ₃	CH ₃	D-glu	C	C	H	OH
A51568		)								I	I		
A	[92182-33-7]	(42)	1	L-van	O	H	H	H	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
B	[92182-32-6]	(43)	2	L-van	O	H	H	H	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
M43		)			H					I	I		
A	[99759-15-6]	(44)	1	L-van	O	CH ₃	CH ₃	CH ₃	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
B	[99776-55-3]	(45)	1	L-van	O	CH ₃	CH ₃	CH ₃	H	C	C	<i>i</i> C ₃ H ₇	OH
C	[99759-14-5]	(46)	1	H	O	CH ₃	CH ₃	CH ₃	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
D	[99759-13-4]	(47)	1	L-van	O	H	CH ₃	CH ₃	H	C	C	<i>i</i> C ₃ H ₇	NH ₂
orienticin		)			H					I	I		
A ^d	[111073-20-2]	(48)	1	4- <i>epi</i> -van	O	H	H	CH ₃	4- <i>epi</i> -van	C	H	<i>i</i> C ₃ H ₇	NH ₂
B	[111073-19-9]	(49)	1	L-oli	O	H	H	CH ₃	4- <i>epi</i> -van	C	H	<i>i</i> C ₃ H ₇	NH ₂
C ^e	[112848-47-2]	(50)	1	4- <i>epi</i> -van	O	H	H	CH ₃	4- <i>epi</i> -van	H	H	<i>i</i> C ₃ H ₇	NH ₂
D	[112848-46-1]	(51)	1	4- <i>epi</i> -van	O	H	CH ₃	CH ₃	4- <i>epi</i> -van	C	H	<i>i</i> C ₃ H ₇	NH ₂
eremomycin ^f	[110865-90-2]	(52)	1	4- <i>epi</i> -van	O	H	H	CH ₃	4- <i>epi</i> -van	H	C	<i>i</i> C ₃ H ₇	NH ₂
A42867	[114540-35-1]	(53)	1	D-tha	O	H	H	CH ₃	van	H	C	<i>i</i> C ₃ H ₇	NH ₂
chloroorienticin		)			H						I		
A ^g	[118395-73-6]	(54)	1	4- <i>epi</i> -van	O	H	H	CH ₃	4- <i>epi</i> -van	C	C	<i>i</i> C ₃ H ₇	NH ₂
B	[118373-81-2]	(55)	1	H	O	H	H	CH ₃	4- <i>epi</i> -van	C	C	<i>i</i> C ₃ H ₇	NH ₂
C	[118373-82-3]	(56)	1	^c	O	H	CH ₃	CH ₃	4- <i>epi</i> -van	C	C	<i>i</i> C ₃ H ₇	NH ₂
D	[118373-83-4]	(57)	1	4- <i>epi</i> -van	O	H	CH ₃	CH ₃	4- <i>epi</i> -van	C	C	<i>i</i> C ₃ H ₇	NH ₂
E	[118373-84-5]	(58)	1	H	O	H	CH ₃	CH ₃	4- <i>epi</i> -van	C	C	<i>i</i> C ₃ H ₇	NH ₂
MM 47761 ^h	[126985-51-1]	(59)	1	rha	O	H	H	CH ₃	4- <i>epi</i> -van	H	C	<i>i</i> C ₃ H ₇	NH ₂
MM 49721	[126985-52-2]	(60)	1	rha	O	H	H	CH ₃	4- <i>epi</i> -van	H	H	<i>i</i> C ₃ H ₇	NH ₂
		)			H								

^a Abbreviations are van = vancosamine, glu = glucose, oli = olivose, 4-*epi* = 4-*epi*-vancosamine, eremo = eremosamine.

^b Identical to K-288.

^c The hydroxyl on ring 4 does not carry any sugar.

^d Identical to UK-72,051.

^e Identical to A82846C, MM 47756.

^f Identical to A82846A, MM 45289.

^g Identical to A82846B.
^h Identical to decaplanin.

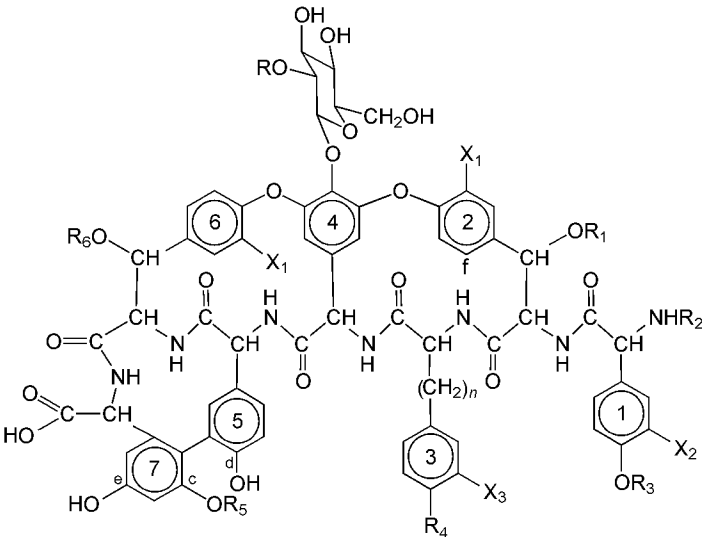


Table 5. Naturally Occurring Actinoidin-type Dalbaheptides

Antibiotic	CASRegistryNu mber	Structure ^a											
		No	<i>n</i>	R	R ₁	R ₂	R ₃	R ₄	R ₅	R	X ₁	X ₂	X ₃
actinoidin													
A	[60382-78-7]	(61)	1	L-aco	H	H	H	H	D-man	L-aca	H	H	H
B	[60382-79-8]	(62)	1	L-aco	H	H	H	H	D-man	L-aca	H	C	H
		)										1	
chloropolysporin													
α	[73957-86-5]	(63)	0	L-ria	D-man	CH ₃	L-rha	O	H	L-ria	H	H	H
		)						H					
β	[73957-87-6]	(64)	0	L-ria	D-man	CH ₃	L-rha	O	H	L-ria	H	H	C
		)						H					1
ε	[88899-52-9]	(65)	0	L-ria	H	CH ₃	L-rha	O	H	L-ria	H	H	C
		)						H					1
chloropolysporin													
B	[105650-11-1]	(66)	0	H	man	CH ₃	rha	O	H	ria	C	H	C
		)						H			1		1
C	[105650-12-2]	(67)	0	H	man	CH ₃	H	O	H	ria	C	H	C
		)						H			1		1
actinoidin A ₂	[108905-13-1]	(68)	1	L-rha	H	H	H	H	D-man	L-aca	H	H	H
		)											
helvecardin													
A	[119979-33-8]	(69)	0	ria	man	CH ₃	O-Me-rha	O	H	ria	H	H	C
		)						H					1
B	[119979-34-9]	(70)	0	ria	H	CH ₃	O-Me-rha	O	H	ria	H	H	C
		)						H					1
MM 4776 ^b	[129772-77-6]	(71)	1	aco	H	CH ₃	H	H	H	aca	H	C	H
		)										1	
MM 55256 ^b	[129652-26-2]	(72)	1	aco	H	CH ₃	H	H	H	aca	H	C	H
		)										1	

^a Abbreviations are aco = acosamine, aca = actinosamine, ria = ristosamine, man = manhose, rha = rhamnose, and O – Me – rha = 2-O-methylrhamnose.
^b These two dalbaheptides differ with regard to the steric position of the terminal NCH₃ group. One O-mannosyl group is present in position 5d, 7c, or 7e.

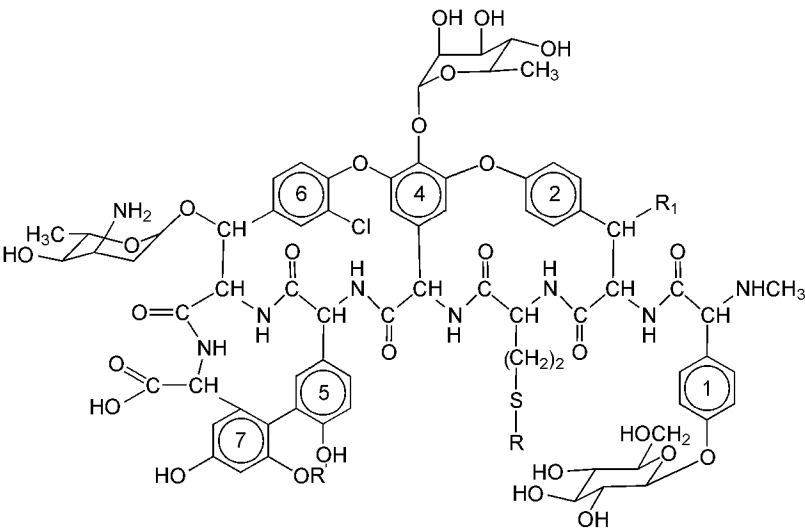


Table 6. Naturally Occurring Dalbaheptides: Symmonicin

Symmonicin	CASRegistryNumber	Structure ^a			Empirical formula
		No.	R	R'	
A	[114836-24-7]	(73)	(O)CH ₃	man	C ₈₀ H ₈ ClN ₈ O ₃₄
B ^b	[114836-22-5]	(74)	CH ₃	man	C ₈₀ H ₈ ClN ₈ O ₃₃
C	[114836-68-3]	(75)	CH ₃	H	C ₇₄ H ₇ ClN ₈ O ₂₈ S

^a Abbreviation is man = mannose.
^b Mixture of two epimers at terminal HC–NH, B' is (R); B'' is (S).

Knowledge of the mechanism of action and investigations on the physico-chemical characteristics of the therapeutically used dalbaheptides has stimulated the transformation of natural antibiotics into new derivatives using both chemical and biosynthetic modification.

Naturally Occurring Dalbaheptides

Vancomycin (39) was introduced into clinical practice much earlier than its structure was elucidated. Structure investigations lasted 25 years (10–12), the structure being definitely assigned in 1983 (13). Structure elucidation of new dalbaheptides is done much faster by the instrumental techniques utilized in the 1990s. Especially helpful are: hplc on new stationary phases (14) (see CHROMATOGRAPHY); high field nmr including two-dimensional (2-D) experiments for structure elucidation (15,59) (see MAGNETIC SPIN RESONANCE); and soft ionization by fast atom bombardment mass spectrometry (qv) (fab ms), which allows determinations of mol wt up to 2500 d with high accuracy (16,17).

Many labeling systems have been used for dalbaheptide structures. The one used herein, where each of the seven amino acids is identified by a number (see Table 2) and each atom by a letter, is widely applied because it permits easy comparison of ¹H and ¹³C nmr data (31). The IUPAC system, utilized in *Chemical Abstracts* and generally in the description of semisynthetic derivatives, requires decodification for comparison of different dalbaheptides (83).

Descriptive Chemistry. Five of the seven amino acids that form the peptidic skeleton are common to all dalbaheptides: amino acid 2 is a tyrosine facultatively β-hydroxylated; amino acids 4 and 5 are *p*-hydroxyphenylglycines; 6 is a β-hydroxytyrosine and 7, the carboxy terminal, is a *m,m'*-dihydroxyphenylglycine. Oxygen bonds between the phenyl moieties of amino acids 2 and 4 and 4 and 6 form two adjacent rings. Another ring is formed by a C–C bond between the phenyl moieties of amino acids 5 and 7. The remaining two amino acids 1 and 3, help to classify all known dalbaheptides into four types. The ristocetin-type (Tables 2 and 3) where amino acid 1, the terminal NH₂, is a *p*-hydroxyphenylglycine and 3 is a *m,m'*-dihydroxyphenylglycine; an ether bond between these phenyl moieties generates an extra ring. The vancomycin-type (Table 4) where amino acids 1 and 3 are aliphatic, usually leucine and asparagine; in OA-7653A,B amino acid 1 is alanine; amino acid 3 is glutamine in OA-7653A (40), A51568B (43), glutamic acid in OA-7653B (41) and aspartic acid in M43B (45). The actinoidin-type (Table 5) where amino acid 1 is always a *p*-hydroxyphenylglycine and amino acid 3 is a phenylalanine or *p*-hydroxyphenylglycine. Only a few dalbaheptides belong to this group. And symmonicin (Table 6) which is the only example of a dalbaheptide where amino acid 1 is aromatic (*p*-hydroxyglycine) and amino acid 3 is a thioamino acid such as methionine.

Dalbaheptides of natural origin have small variations in the nature and position of substituents. Additional chemical features are (1) chlorine atoms (up to four), methyl, and additional hydroxyl groups that can be present in different positions in the phenyl residues. No chlorine is present in ristocetins (1), (2), orienticin C (50), or MM 49721 (60). (2) Simple or complex carbohydrates that are linked to the core peptide in one or more positions through hemiacetalic bonds. Sugars found in dalbaheptides can be neutral, basic, or acidic. Vancosamine, *epi*-vancosamine, ristosamine, actinosamine, and acosamine were first isolated from dalbaheptides. A41030A (11), B (12), E (14), and A47934 (16) do not carry any sugar; minor amounts of partially (pseudoaglycones) or totally (aglycones) deglycosylated dalbaheptides are often present in many normally recovered batches. These compounds can be natural metabolites or artifacts of the recovery and purification processes. (3) A phenolic hydroxyl is esterified as a sulfate monoester in A47934 (16) and UK-68,597 (17). (4) The terminal carboxyl in ristocetin and actaplanin is a methyl ester and the terminal amino group can be methylated. In UK-68,597 (17) the *N*-terminal residue is replaced by a ketoamide functionality. (5) The amino group of glucosamine or 2-amino-2-deoxyglucuronic acid linked to the *p*-hydroxyphenyl residue of amino acid 4 of some ristocetin-type dalbaheptides is acylated by 10–12 carbon fatty acid residues. The acyl chains may be linear or branched (iso or anteiso), only exceptionally unsaturated. Acyl derivatives are present in teicoplanins, ardacins, A40926, kibdelins, and parvodicens and are therefore subgrouped as lipidalbalbaheptides (Table 3). The side chains differentiate the components of each complex.

Producing Organisms. All the dalbaheptides so far described are produced by strains belonging to the order of *Actinomycetales* (Table 1). Additionally, co-fermentation of *Actinoplanes missouriensis* NRRL 15647 and strain NRRL 15646, which was obtained by chemical mutagenesis of an actaplanin-producing strain, yielded antibiotic CUC CSV, an actaplaninlike dalbaheptide having a C=O function instead of the terminal HC–NH (84). An *Actinoplanes teichomyceticus* mutant yielded high levels of two teicoplaninlike compounds, designated RS-3 and RS-4, carrying 6-methyloctanoic and *n*-nonanoic vesiolues as fatty acid chains (85,86).

Screening. The dalbaheptides were at first isolated by conventional screening procedures. More recently mechanistically based screens have been devised. For example, bioselective adsorption on affinity resins made by immobilizing *N*-acetyl-D-Ala-D-Ala [19993-26-1] on an activated support (87,88) was used in a screening campaign in which 72 strains were identified as producers of dalbaheptides, 60% of which produced ristocetin (89). The other characterized dalbaheptides were teicoplanins (Table 3), avoparcins (Table 5), actaplanins (Table 2), and the novel molecules A40926 (Table 3) and A42867 (53).

Other specific discovery assays have been used such as differential inhibition of a vancomycin resistant *S. aureus* strain and its susceptible parent, and an assay based on antagonism of the antibacterial activity by *N,N*-diacetyl-L-Lys-D-Ala-D-Ala [24570-39-6], a tripeptide analogue of the dalbaheptides receptor. Application of this latter test to 1936 cultures (90) led to the isolation of 42 dalbaheptides, six of which, including kibdelin (Table 3), parvodicin (Table 3), and actinoidin A₂ (68) were novel. A colorimetric assay based on competition between horseradish peroxidase bound teicoplanin and the

putative dalbaheptide for a D-Ala-D-Ala peptide attached to the test tube wall has also been utilized (89,91) as has a polyclonal antibody against vancomycin, an enzyme-linked immunosorbent analysis (ELISA), which led to the discovery of A82846 (68).

Fermentation. Dalbaheptides are produced by submerged fermentation (qv) and this topic has been reviewed (92). In a few cases addition of a biosynthetic precursor of the core aglycones such as tyrosine and *p*-hydroxyphenylglycine, increased the yields (39). It has been reported (93) that the fatty acid moieties of teicoplanin (Table 3) biosynthetically derive from the degradation of long-chain fatty acids present in the membranes of the producing microorganisms. Addition to fermentation media of precursors that alter the membrane fatty acid composition led to an altered ratio of the components of teicoplanin (94,95) and A40926 (96).

Recovery and Purification. The dalbaheptides are present in both the fermentation broth and the mycelial mass, from which they can be extracted with acetone or methanol, or by raising the pH of the harvested material, eg, to a pH of 10.5–11 for A47934 (16) (44) and A41030 (41) and actaplanin (Table 2) (28). A detailed review on the isolation of dalbaheptides has been written (14). Recovery from aqueous solution is made by ion pair (avoparcin) or butanol (teicoplanin) extraction. The described isolation schemes use ion-exchange matrices such as Dowex and Amberlite IR, acidic alumina, cross-linked polymeric adsorbents such as Diaion HP and Amberlite XAD, cation-exchange dextran gel (Sephadex), and polyamides in various sequences. Reverse-phase hplc, ion-exchange, or affinity resins may be used for further purification (14,89).

Physical Properties. The molecular weight of dalbaheptides ranges from about 1150 to 2200. Pure dalbaheptides are obtained as colorless or whitish amorphous powders that usually retain water and solvent. Dalbaheptides are generally water-soluble. Teicoplanin can be obtained as an internal salt or as a partial monoalkaline (sodium) salt depending on the pH of the aqueous solution in the final purification step. Other dalbaheptides are obtained as acidic salts, such as hydrochlorides (vancomycin, actaplanin) or sulfates (ristocetin A, avoparcin, eremomycin). The presence of amino, carboxyl, benzylic, and phenolic hydroxyl functions, sugars, and aliphatic chains influence both water solubility and total charge. Aqueous solutions of vancomycin (39) at pH 3–5 and of teicoplanins (Table 3) at pH 7.4 are stable. The isoelectric points (pI) of dalbaheptides, determined by electrofocusing, vary from 3.2 for A47934 (16) to 8.1 for ristocetin (Table 2), A477, and A42867 (53). The lipid–water partition coefficient in *n*-octanol buffer is 1.1 at pH 5.1 for teicoplanin (Table 3) and 2.5 for vancomycin (39) indicating that teicoplanin is 5–10 times less hydrophilic than vancomycin.

Dalbaheptides are levorotatory. The absolute configuration of vancomycin was determined by x-ray analysis of degradation product CDP-I [79517-31-0] (11). The configurations of the seven amino acids are 1(R), 2(R), 3(S), 4(R), 5(R), 6(S), and 7(S) (Table 2). Nmr experiments provided evidence that the stereochemistry of the chiral centers and the overall three-dimensional conformation is the same for most dalbaheptides. Natural and chemically produced epimers are exceptions. The anomeric conformation and position of the sugars have also been determined by nmr. In teicoplanin five of the conformations of the amide linkages are trans, the 5–6 linkage is cis. The stereostructure of teicoplanin aglycone is shown in Figure 1.

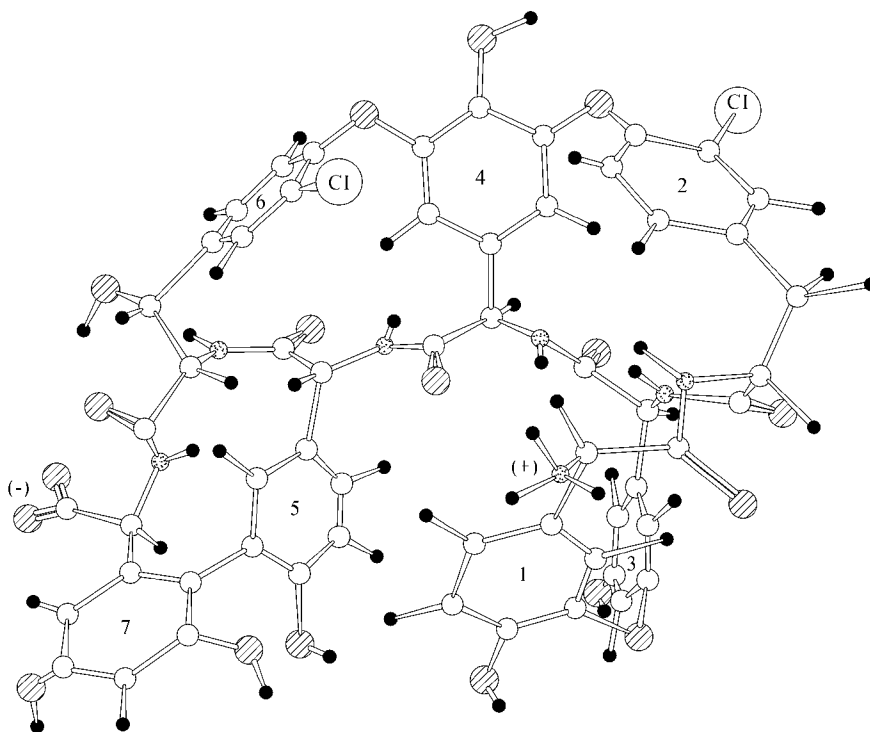


Fig. 1. Stereostructure of teicoplanin aglycone [89139-42-4] obtained from a Dreiding model (83) where ● is hydrogen, ⊙ is nitrogen, ○ is carbon, ⊗ is oxygen. The numbers represent the seven amino acids.

Biosynthesis. Biochemical studies on dalbaheptides have been reviewed (92,97). Experiments with ^{13}C and ^2H have shown that in vancomycin (39), D-tyrosine is the precursor of D-*p*-hydroxyphenylglycine and β -hydroxy-*m*-chlorotyrosine, and acetate the precursor of the two *m,m'*-dihydroxyphenylglycines (98). Similar results using either ^{13}C or radioactively labeled material have been reported for avoparcin (Table 5) (23), ristocetin (Table 2) (99,100), ardacin (Table 3) (101), and A47934 (102).

Kibdelins (Table 3) are converted into the corresponding ardacins by cultures of *Kibdelosporangium aridum* indicating that the oxidation of carbon-6 of glucosamine to a carboxy group is the last biosynthetic step (100). Addition of ^{14}C -labeled ardacin aglycone to cultures of *K. aridum* gave origin to labeled ardacins but the yields were so low it is doubtful that the aglycone is the precursor of the glycosylated product. Other studies showed that the sulfate ester on phenolic hydroxyl in the production of A47934 (16) occurs prior to the formation of microbiologically active intermediates (102).

Biological Properties

Mechanism of Action. The basis of the antibacterial action of dalbaheptides is the ability to form a complex with the terminal D-Ala-D-Ala residues of growing peptidoglycan chains, thus preventing transglycosylation, eg, chain elongation, and transpeptidation, eg, cross-linking. The consequent defective cell wall stops bacterial growth and eventually leads to cell death. The mechanism of action has been reviewed both at the molecular (3) and at the biochemical level (4). Addition of a dalbaheptide to a growing culture results in rapid inhibition of incorporation of acetylglucosamine, a specific precursor of cell wall synthesis, and in accumulation of UDP-N-acetylmuramyl pentapeptide. Direct interaction studies of dalbaheptides and D-Ala-D-Ala-containing synthetic peptides have been carried out. Binding of dalbaheptides to D-Ala-D-Ala models has been measured by uv differential spectroscopy (3), affinity chromatography (87), microcalorimetry (103), nmr spectrometry (104), displacement of polyacrylamide-bound vancomycin (39) (105), and displacement of radiolabeled ristocetin bound to bacterial cells (106). These studies indicate that a free carboxyl and a D-configuration of the terminal amino acid of the model peptide are absolute requirements for formation of the complex. Stereostructure of the dalbaheptide skeleton forms a sort of receptor pocket which accommodates the D-Ala-D-Ala terminus of the target (3,107).

Antibacterial Activity.

In Vitro Properties. The antibacterial spectrum of most dalbaheptides is known (Table 1). Vancomycin (39) and or teicoplanin (Table 3) are generally introduced as reference compounds. Direct comparative data for some dalbaheptides tested under the same experimental conditions are given in

Table 7 (54).

Table 7. Antibacterial Activity of Dalbaheptides, MICs in µg/mL^a

Antibiotic	Organism and strain					
	<i>Staphylococcus aureus</i> TOUR	<i>Staphylococcus epidermidis</i> ATCC 12228	<i>Streptococcus pyogenes</i> C 203	<i>Enterococcus faecalis</i> ATCC 7080	<i>Clostridium perfringens</i> ISS 30543	<i>Neisseria gonorrhoeae</i> ISM 68/126
ristocetin ^b	4	2	0.25	1	2	64
vancomycin ^c	0.25	0.5	0.13	0.5	0.13	32
avoparcin ^d	2	2	0.25	0.25	0.5	128
actaplanin ^b	1	2	0.13	0.5	1	>128
teicoplanin ^e	0.13	0.13	0.06	0.13	0.03	32
A35512B ^b	1	0.5	0.13	0.5	2	64
A41030 ^b	0.03	0.008	0.13	0.13		64
A47934 ^b	0.06	0.03	0.13	0.13	0.25	8
ardacin ^e	1	4	0.13	2	0.06	64
A40926 ^e	0.06	0.06	0.06	0.06	0.004	2

^a From Ref. 54 and the Author's Laboratory.

^b Structures shown in Table 2.

^c Structure (39).

^d Structures shown in Table 5.

^e Structures shown in Table 3.

Dalbaheptides are active almost exclusively against gram-positive microorganisms including all major pathogens such as *staphylococci*, coagulase-positive and negative, *streptococci* of all groups, *enterococci* including *E. faecalis* and *faecium*, *corynebacteria* including JK and *acnes*, *Clostridia* including *C. perfringens* and *C. difficile*, anaerobic cocci eg, *peptococci* and *streptostreptococci*, and *Listeria monocytogenes*. Gram-positive organisms naturally resistant to dalbaheptides include *Lactobacilli*, *Leuconostoc*, *Pediococcus*, and *Nocardia*. Lipodalbaheptides are in general less active than other dalbaheptides against CNS. For example, the MIC against *S. haemolyticus* is from 4 to 50 µg/mL.

Gram-negative organisms are unsusceptible except *Gardnerella vaginalis* and *Branhamella catarrhalis* which are susceptible to teicoplanin, and *Neisseria gonorrhoeae* (Table 7). However, A47934 and A40926 (54) are exceptionally active against *N. gonorrhoeae*, having MICs of 8 and 2 µg/mL, respectively.

In the parvodicin and teicoplanin series (Table 3) the nature and length of the fatty acid portion of the glycolipid moiety only slightly influence the activity *in vitro*. Dalbaheptides are bactericidal against actively growing, but not against resting, bacteria (33).

In Vivo Properties. The efficacy of dalbaheptides has been assessed in various models of experimental *septicemia* in mice. In general there was good correlation between the ED₅₀s (effective doses which prevent death in 50% of test animals) and the MICs on test strains. Teicoplanin was very effective, ED₅₀ values ranged from 0.11 to 0.72 mg/kg sc administration for septicemias caused by *S. pyogenes*, *S. pneumoniae*, and *S. aureu*, whereas for vancomycin ED₅₀s were from 0.58 to 7.2 mg/kg (33). Eremomycin (52) had therapeutic activity 2–3 times greater than vancomycin. Therapeutic indices for staphylococcal–streptococcal sepsis exceeded ten times those of vancomycin (8). Ardacin and kibdelin are less active *in vivo* than vancomycin, although the MIC on the tested strains are comparable. This happens also for A40926 in respect to teicoplanin (54). In fact, the long lasting ardacin was more active than vancomycin when administered as early as 18 h before infection (48). Teicoplanin and vancomycin were also found to be active against experimentally induced endocarditis in rabbits (108) and rats (109), and against localized infection in mice (109).

Pharmacokinetics. Pharmacokinetic studies in mice via iv administration have been done mainly on vancomycin (39), eremomycin (52), and lipodalbaheptides (Table 3). A systematic investigation of the relationship between pI, lipophilicity, and pharmacokinetic parameters of ardacin and its hydrolysis products in comparison to those of ristocetin (Table 2), teicoplanin, and vancomycin has been carried out (110). Ardacin and its pseudoaglycone having pIs ≈3.8 yielded high and prolonged serum concentrations and the half-life ranged from 226 to 492 min. In contrast, vancomycin and ristocetin, which have pIs ≈8, had t_{1/2} = 20 and 62 min, respectively; teicoplanin and ardacin aglycone, pIs ≈5, had intermediate elimination rates, t_{1/2} ranged from 118 to 155 min. For dalbaheptides having similar pIs, clearance decreased and half-life increased as lipophilicity increased.

Mechanism of Resistance. Recently, resistance to high levels of dalbaheptides has been described in both *E. faecium* and *E. faecalis* (111). This resistance, inducible by low concentrations of dalbaheptides, is plasmid mediated and is transferable. Concomitant with the induction of resistance is the appearance or increased expression of a protein having a molecular weight of either 39,500 or 39,000. The enzymatic activity of this material has been postulated (112). Although the mechanism of resistance induction by dalbaheptides is unknown, different dalhahaheptides have different induction capacity. Vancomycin (39) is the most powerful inducer; teicoplanin is a very weak inducer.

Chemical Modifications

Although it has been known for some time that hydrolysis of ristocetin leads to derivatives having different or increased antimicrobial activity (113), little chemical modification work was reported in the literature until the mid-1980s. Selective removal of sugar moieties and glycosylation, deacylation, deamination, dechlorination, introduction of bromine or chlorine atoms, esterification or amidation of the terminal carboxyl, acylation or alkylation of the terminal (or sugar) amino groups have all since been described, mainly in patent applications. Some of the aglycones and pseudoaglycones showed a weak activity against selected gram-negative bacteria (83,114,115). Among the most interesting compounds produced was SKF 104662 [121089-14-3], obtained from the B' epimer of symmonicin (Table 6) after selective removal of the neutral sugars and glycosylation of the hydroxyl on ring 4 (116). The *in vitro* activity (117) and therapeutic efficacy in experimental infection in mice for SKF 104662 were similar to vancomycins or teicoplanins. SKF 104662 was less toxic than vancomycin in mice and the pharmacokinetic profile in mice, rats, and dogs indicated that the half-life was also longer than that of vancomycin (118).

The -NH(CH₂)₃N(CH₃)₂ amide of teicoplanin factor A2-2, coded MDL 62,873 [122173-74-4], was also prepared. The combined effect of a moderate basicity and a slightly increased lipophilicity at neutral pH probably led to a better penetration through the cell wall. MDL 62,873 was consistently more active than teicoplanin against CNS clinical isolates (119,120). No semisynthetic dalbaheptide is under clinical evaluation at this writing.

Economic Aspects

Only three dalbaheptides are commercialized: vancomycin (39) and teicoplanin (18–22) for human health, and avoparcin (63–65) for animal usage. Vancomycin, the main trademark of which is Eli Lilly's Vancocin had 1990 sales around \$160 million. Total annual production is in the vicinity of 8 t. Teicoplanin, trademarked Targocid, had 1990 sales of \$35 million corresponding to 200 kg. Teicoplanin is commercialized in Europe, Hong Kong, Korea, and the Middle East. It is at the late developmental clinical phase in North America and Japan. Avoparcin is used as a growth promoting feed additive (see FEEDS AND FEED ADDITIVES; GROWTH REGULATORS).

Clinical Use. Vancomycin and teicoplanin as formulated drugs are lyophilized powders to be reconstituted with sterile water for injection. Vancomycin hydrochloride [1404-93-9], is presented in vials of 500 mg that give 100–200 mL solution of pH 2.5–4.2. It is administered by slow (60 min) infusion at a dose of 500 mg every 6 h or 1 g every 12 h/d. The teicoplanin contains the five factors (87%) plus 13% of the pseudoaglycone T-A3-1. It is presented in vials containing 200 mg of lyophilized power that after dissolution with 3 mL of solvent gives a solution at pH 7.5. The dose regimen is 200–800 mg/d by iv bolus administration.

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